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RELATION OF LESIONS OF THE TONGUE IN CHILDREN TO NIACIN DEFICIENCY

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ONE of the principal manifestations of pellagra is an alteration in the appearance of the tongue. According to reports in the literature,[1] this alteration may be the sole clinically recognizable sign of niacin (nicotinic acid U. S. P.) deficiency. It has been reported also that the administration of niacin leads to the return of the tongue to its normal appearance.[2] The object of this investigation was to determine to what extent certain types of changes in the tongue in children may be influenced by niacin therapy.

Abnormalities in the appearance of the tongue are common during childhood. During the four year period from 1942 to 1945, 225 children with changes in the tongue were seen in the wards and in the outpatient department of the children's medical service, Bellevue Hospital. Of these children, 60 were observed over an extended period, and these observations form the basis of this report.

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1. (*a*) Kruse, H. D.: The Lingual Manifestations of Aniacinosis, with Especial Consideration of the Detection of Early Changes by Biomicroscopy, Milbank Mem. Fund. Quart. **20**:262, 1942. (*b*) Jolliffe, N., and Stern, M.: Objective Manifestations of Nutritional Deficiency Diseases, Clinics **1**:282, 1942.

2. Footnote 1. Sevringhaus, E. L., and Kyphos, E. D.: Reversal of Lingual Atrophic Changes with Nicotinamide Therapy, Arch. Int. Med. **76**:31 (July) 1945.

RELATION OF CHANGES IN THE TONGUE TO DEFICIENCY STATES

Changes in the tongue have been described in association with deficiencies in niacin, riboflavin, pyridoxine and biotin. In pellagra there is at first a swelling of the papillae at the tip and on the lateral aspects of the tongue, with redness of the buccal mucosa. As the disease progresses, the entire tongue and all the oral mucous membranes become bright red. Ulcerations may appear anywhere in the mouth, with a predilection for the under surface of the tongue.[3]

According to Spies, Bean and Stone,[4] administration of large amounts of niacin, niacinamide or nikethamide ("coramine") to 73 persons with pellagra resulted in fading of the lesions of the mucous membrane as well as blanching of the erythema of the cutaneous lesions, disappearance of mental symptoms and decrease or cessation of the porphyrinuria within seventy-two hours.

The tongue of a person with riboflavin deficiency[5] resembles that of a person with niacin deficiency except that it has a magenta hue, the epithelium does not desquamate and the papillae are flattened, giving a pebbled appearance. The lesion responds to administration of riboflavin supplements. Changes in the tongue have been described which failed to respond to niacin or to riboflavin but which improved strikingly with administration of pyridoxine.[6]

Lesions of the tongue have been observed in patients maintained on diets poor in all known vitamins of the B group except riboflavin and supplemented with adequate amounts of the available members of the vitamin B complex. In these diets at least 30 per cent of the total calories was supplied by desiccated egg white.[7] The changes in the tongue varied from the geographic type to general atrophy of the lingual papillae or marginal atrophy of the tongue. Cure resulted in three to five days with administration of 150 to 300 micrograms of biotin per day.

Changes in the tongue occur in many other diseases in which there is reason to believe that nutritional deficiency exists. Atrophy of the lingual papillae, giving rise to smoothness of the tongue, is seen in

3. Spies, T. D., and Cooper, C.: The Diagnosis of Pellagra, Internat. Clin. **4**:1, 1937.

4. Spies, T. D.; Bean, W. B., and Stone, R. E.: The Treatment of Subclinical and Classic Pellagra, J. A. M. A. **111**:584 (Aug. 13) 1938.

5. Sydenstricker, V. P.: The Clinical Manifestations of Nicotinic Acid and Riboflavin Deficiency (Pellagra), Ann. Int. Med. **14**:1499, 1941.

6. Rosenblum, L. A., and Jolliffe, N.: The Oral Manifestations of Vitamin Deficiencies, J. A. M. A. **117**:2245 (Dec. 27) 1941.

7. Sydenstricker, V. P.; Singal, S. A.; Briggs, A. P.; DeVaughn, N. M., and Isbell, H.: Observations on the "Egg White Injury" in Man, J. A. M. A. **118**: 1199 (April 4) 1942.

association with pernicious anemia,[8] sprue [9] and other intestinal disorders,[10] microcytic hypochromic anemia [11] and the anemia of pregnancy.[12] The lesions of the tongue generally improve or disappear entirely with correction of the underlying disease process. According to Minot and Murphy,[8] there was complete remission of the glossitis in patients with pernicious anemia who received liver. Isaacs and co-workers [13] noted a mild recurrence of glossitis even while patients were receiving liver therapy, and they therefore concluded that liver was not specific for this lesion. Jolliffe and Stern [1b] also saw patients with pernicious anemia whose tongues failed to improve with the administration of liver or with a good diet although the hematologic response was satisfactory. The addition of niacin resulted in gradual improvement and cure within a year.

Rhoads [14] reported the occurrence of atrophic glossitis in patients with pneumonia treated with sulfanilamide which was cured with vitamin B complex therapy. He also described cases of stomatitis, associated with achlorhydria in some instances, in which the condition improved on administration of these vitamins.

MILD CHRONIC NIACIN DEFICIENCY STATES

In recent years mild changes in the tongue in children and adults have been ascribed to niacin deficiency. Spies and co-workers [4] stated that a slowly progressing deficiency in the antipellagra factor commonly exists in the children of persons with pellagra and that definite evidence of pellagra develops later.

In adults, Jolliffe and Stern [1b] described a chronic but mild form of niacin deficiency, manifested by periods of soreness of the tongue, increased redness of the tip and margins and areas of papillary atrophy. Response to therapy was slow, one to three months of treatment being

8. Minot, G. R., and Murphy, W. P.: A Diet Rich in Liver in the Treatment of Pernicious Anemia: Study of One Hundred and Five Cases, J. A. M. A. **89**: 759 (Sept. 3) 1927.

9. Castle, W. B., and Rhoads, C. P.: The Aetiology and Treatment of Sprue in Porto Rico, Lancet **1**:1198, 1932.

10. Keefer, C. S., and Yang, C. S.: Anemia of Undernutrition, Nat. M. J. China **15**:701, 1929. Hutter, A. M., and Middletown, W. S.: Vitamin B Deficiency and the Atrophic Tongue, J. A. M. A. **101**:1305 (Oct. 21) 1933.

11. Wilkinson, J. F., and Oliver, T. H.: Some Clinical Conditions Associated with Achlorhydria, Lancet **1**:66, 1931. Witts, L. J.: Chronic Microcytic Anemia, Brit. M. J. **2**:883, 1931.

12. Larrabee, R. C.: The Severe Anemias of Pregnancy and the Puerperium, Am. J. M. Sc. **170**:371, 1925.

13. Isaacs, R.; Sturgis, C. C., and Smith, M.: Treatment of Pernicious Anemia, J. A. M. A. **91**:1687 (Dec. 1) 1928.

14. Rhoads, C. P.: Conference on Therapy: Vitamin B_2 Therapy, J. A. M. A. **113**:297 (July 22) 1939.

required before the appearance of definite papillary regeneration. Often a year or more of therapy was necessary before complete disappearance of atrophy.

According to Kruse,[15] the mild, chronic changes in the tongue of aniacinosis have gone unrecognized. He stated that a high prevalence of aniacinosis exists, principally owing to the prolonged use of deficient diets. Also, certain factors, both external and internal, such as rate of growth, pregnancy, lactation, work, sunlight, climate, toxic materials and disease, may affect the supply of or increase the requirements for niacinamide above the basal level. In his opinion, ariboflavinosis, avitaminosis A and avitaminosis C resemble aniacinosis in their slow response to therapy.

Martin and Koop [15] described lesions of the tongue in adults similar to those which we have observed in children. They gave niacin or preparations of the vitamin B complex to patients with glossitis migrans and fissured tongue and concluded that glossitis migrans does not respond to either therapy and that the fissuring of the tongue and other lesions respond better to the whole vitamin B complex than to niacin alone.

Field and co-workers [16] stated that in the northern part of this country the only change in the pellagrous tongue is atrophy. They treated many patients with niacinamide and vitamin B complex concomitantly, with pronounced improvement.

In patients with pellagra, Kuo and Huang [17] reported that the acute manifestations of glossitis responded promptly to niacin treatment, but that the underlying chronic atrophic lesions were affected only by administration of liver extract intramuscularly. In other patients the atrophic glossitis did not respond in one week to niacin, but liver therapy improved the condition in ten to thirty-three days. It is not stated whether the improvement was maintained.

In 4 patients Spies and co-workers [18] were unable to influence the fissuring of the tongue with niacin therapy.

ANATOMY OF THE TONGUE

The tongue consists of interlacing bundles of striated muscle covered with a closely adherent mucous membrane. The upper surface and the margins of the anterior two-thirds are covered with papillae, of which there are four types: fili-

15. Martin, H., and Koop, C. E.: The Precancerous Mouth Lesions of Avitaminosis B, Am. J. Surg. **57**:195, 1942.

16. Field, H.; Parnall, C., and Robinson, W. D.: Pellagra in the Average Population of the Northern States, New England J. Med. **223**:307, 1940.

17. Kuo, P. T., and Huang, M. S.: Nutritional Stomato-Glossitis Among the War Refugees in Shanghai, Chinese M. J. **59**:430, 1941.

18. Spies, T. D.; Cooper, C., and Blankenhorn, M. A.: The Use of Nicotinic Acid in the Treatment of Pellagra, J. A. M. A. **110**:622 (Feb. 26) 1938.

form, fungiform, circumvallate and foliate. The filiform papillae are 2 to 3 mm. long.[19] Their core is a connective tissue ridge, covered with numerous secondary papillae with pointed ends. Fungiform papillae reach a height of 0.7 to 1.8 mm. and a thickness of 0.4 to 1 mm. These papillae have a short, slightly constricted stalk and a spherical, flattened upper part. The connective tissue core forms many secondary papillae. The epithelium covering them has a smooth, free surface. On many, but not all, of the fungiform papillae the epithelium contains eight to ten taste buds. As the core is rich in blood vessels, the fungiform papillae are red. The circumvallate papillae are sunk into the surface of the mucous membrane parallel to and in front of the V-shaped sulcus terminalis, and each is surrounded with a deep circular furrow. The covering epithelium is smooth, while the epithelium of the lateral surfaces of the papillae contains many taste buds. Foliate papillae are located on the lateral margins of the tongue just in front of the glossopalatine arch and lateral to the circumvallate[20] papillae. They are variable in number, usually four to eight, and they consist of vertical folds separated by grooves, which do not project far above the surface of the tongue. The posterior third, or the pharyngeal portion, of the tongue is devoid of papillae, but is thickly studded with small, irregular projections, each with a small pit just visible to the eye. These projections are lymphoid follicles, continuous on each side with the lymphoid tissue of the tonsil.[21]

TYPES OF LESIONS OF THE TONGUE SEEN IN CHILDREN

Several types of lesions of the tongue are seen in children: acute glossitis, glossitis migrans, mild, chronic swelling of the tongue and fissures of the tongue.

Acute Glossitis.—The tongue is red, swollen and covered with exudate. A child with this condition is acutely ill, and there is fever. There were 5 patients in our series with this condition. In 1 patient (figure, *1 a* and *b*) the glossitis was associated with herpetic stomatitis; in another, with acquired syphilis. In all 5 instances an underlying lesion of the tongue was evident after the acute inflammation had subsided. Mild glossitis, with swollen, red fungiform papillae and a decrease of filiform papillae, is sometimes seen with herpetic stomatitis and generally subsides completely within a few days.

Glossitis Migrans.—A common lesion of the tongue in children is that variously referred to as glossitis migrans, geographic tongue or wandering rash tongue (figure, *2*). The tongue shows reddish, sharply demarcated, irregularly outlined areas, in which the filiform papillae are absent and the fungiform papillae are visible as prominent red dots. Often the reddish areas are surrounded with a whitish border made up of coalesced filiform papillae and debris. The lesions occur intermit-

19. Maximow, A. A., and Bloom, W.: A Textbook of Histology, ed. 4, Philadelphia, W. B. Saunders Company, 1942, p. 360.

20. Spalteholz, W.: Hand Atlas of Human Anatomy, ed. 2, Philadelphia, J. B. Lippincott Company, 1900-1903, vol. 3, p. 493.

21. Fitzwilliams, D. C. L.: The Tongue and Its Diseases, London, Oxford University Press, 1927, p. 1.

Explanation of Plate

1 a, acute glossitis in a boy 8 years of age, who had a sore mouth and throat, with low grade fever for five days. The gums were reddish blue, swollen and tender. The tongue appears swollen, red and tender. On the middle and posterior thirds there is a white, raised, filiform coat, with herpetic lesions in the same area. The white coat extends toward the anterior third of the tongue, but the most striking changes are the irregularly red areas, between which there are small, circular, white, raised herpetic lesions.

1 b, eight days later. The acute process has cleared, revealing an underlying chronic lesion of the tongue. The tongue is less swollen; fissures are present, extending from the margins toward the center of the tongue in a radiating pattern. In the same area the filiform papillae are diminished. The fungiform papillae stand out as red dots outlining the length of the fissures. The margins of the tongue are devoid of filiform papillae.

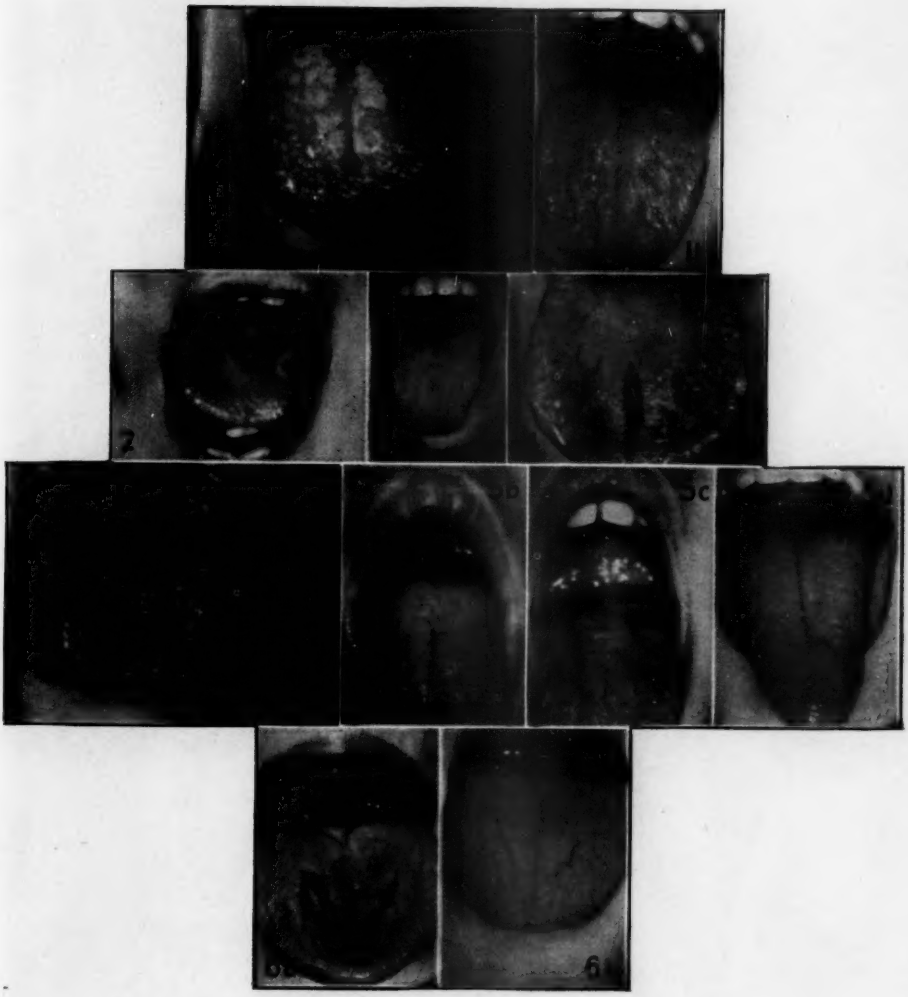
2, glossitis migrans in an 18 month old girl. Migratory lesions of the tongue had been observed since the patient was 10 months of age. The anterior two thirds of the tongue is red, owing to loss of filiform papillae and swelling of the fungiform papillae. This portion is demarcated from the posterior third by a raised, white border. There are two red areas on the margins which are devoid of filiform papillae and in which the fungiform papillae are swollen. Niacinamide therapy, in a dosage of 200 to 300 mg. daily for sixteen months, was without effect.

3, mildly swollen tongue in an 11 year old girl. The slight swelling is manifested by the irregular margins, with tooth impressions. The margins are smooth, red and shiny. The fungiform papillae on the tip of the tongue are swollen and red. The filiform papillae are scattered sparsely over the rest of tongue. There is a slight transverse fissure in the center of the tongue.

4, fissured tongue in an 11 year old Puerto Rican boy with a history of active rheumatic fever and carditis at the age of 10 years. The tongue is large, flat and thin, with marginal tooth indentations. Large, radiating fissures extend from the margins to the center of the tongue. In the same area there is increased redness, with decrease of filiform papillae in size and number and increase in large, red fungiform papillae. In the centers of the fissures there are no filiform papillae.

5, familial occurrence of fissured tongue. (*a*) mother, aged 34; (*b*) boy, aged 13 years; (*c*) boy, aged 12 years, and (*d*) boy, aged 10 years. The tongues are large, with irregularly fissured surfaces. The fungiform papillae are swollen and edematous. The filiform papillae on the anterior half and the margins of the tongue are decreased in size and number.

6, favorable response to treatment with niacinamide in a boy 14 years of age. (*a*) Before treatment. The tongue is swollen and red at the margins and at the tip. In these areas the filiform papillae are decreased and the fungiform papillae are red and swollen. There are central and marginal fissures, in some of which the filiform papillae are absent. (*b*) After treatment with 100 mg. daily for twenty-two months and 400 mg. daily for ten months. The tongue is no longer swollen, and the anterior third shows an increased number of filiform papillae. The fungiform papillae are still large in this area, but they are not so swollen or so red as formerly. The margins remain without filiform papillae. The most striking change is in the fissures, which have become much smaller and are beginning to fill with papillae.


2
3b
3c
6

tently and may be present anywhere on the dorsum or the sides of the tongue. This condition appears early in life (our youngest patient was 4 months of age) and recurs over a period of years.

Mild Chronic Swelling of the Tongue.—In some patients there is slight swelling of the tongue, with enlargement of the fungiform papillae at the tip and decrease of the filiform papillae in some areas (figure, *3*). The filiform pattern is matted in the center and posteriorly. The lateral margins are smooth, with tooth impression, and there is usually a central fissure.

Fissured Tongue.—Fissuring of the tongue is frequent in childhood (figure, *4*). In this condition the tongue is swollen; its margins are smooth and show shallow fissures and tooth impressions. The dorsal surface is broken by fissures, which usually are tranverse but may run in irregular directions. In many instances the anterior half of the tongue is red, owing to swollen, congested fungiform papillae.

In some instances the tongue is greatly enlarged. There are flattening of the filiform papillae and prominence of the fungiform papillae on the margins and the anterior half of the tongue. Occasionally the fungiform papillae coalesce, appearing as large red dots. Fissures are present on the margins and in the center of the tongue, usually in a radiating pattern. The fissures are devoid of papillae and may be wide and deep. In addition, there may be circumscribed, denuded areas, similar to those seen in glossitis migrans. These areas are often painful.

SYMPTOMS

Except in cases of acute glossitis, subjective complaints were uncommon in the present series. Pain was infrequent, but when present it disappeared promptly with treatment. Several children remarked that the tongue "felt smaller" and that their usual food tasted different. Often, after treatment for many months, the patient complained of a burning sensation at the tip of the tongue with certain foods, notably orange juice and spinach. This sensation was temporary.

It is of interest that more patients had complaints concerning the tongue while receiving niacinamide therapy than before. Children in the control (untreated) group also remarked on changes in pain sensation and in the taste of food during the period of observation.

METHOD OF STUDY

Histories were obtained with particular reference to diet, present and past illnesses, growth and development. Examination included, in addition to the usual procedures, a search for evidence of deficiency disease, such as cheilosis, neuritis, cutaneous disorders, photophobia and anemia. Of the 60 patients, 2 had fissures at the corners of the mouth in addition to the lesions of the tongue.

The tongues were inspected at varying intervals, depending on the rapidity of the change. At each visit drawings, notes and color photographs of lesions of the tongue were made. Any illness occurring between visits was also noted.

Therapy.—The 60 patients were divided into two groups—a control and a treated group. Patients in the treated group received from 200 to 600 mg. of niacinamide per day, depending on their age and weight.[22] The 30 patients in the control group received a placebo (lactose pill).

The schedule of daily doses is shown in table 1. No untoward reaction was observed.

FACTORS INFLUENCING THE APPEARANCE OF LESIONS OF THE TONGUE

Diet.—A dietary history was taken when the patient was first seen and at repeated intervals throughout the period of study. The usual method of calculating diets for one week did not seem feasible, for the

TABLE 1.—*Schedule of Daily Doses*

Weight of Patient, Pounds	Niacinamide, Mg. per Day
4 - 39	200
40 - 79	300 - 400
80 -130	400 - 600

TABLE 2.—*Daily Requirements of Niacin During Childhood* *

Age, Yr.	Niacin, Mg. per Kg. Body Weight
Under 1	4
1 to 3	6
4 to 6	8
7 to 9	10
10 to 12	12
Over 12	14 to 20

* These quantities are those recommended by the Food and Nutrition Board of the National Research Council.

following reasons: Our patients came from a low income group; hence, the varying cost of food determined the intake to a large extent. Another limiting factor was war rationing. In many instances the mother was employed outside the home, and the father was in the armed forces; hence the dietary intake was largely uncontrolled.

The daily niacin requirements during childhood are not known with any accuracy. Butler [23] stated that the methods for estimating the amount of this vitamin in the blood and urine are so recent that any detailed discussion of the correctness of their allowances is unwarranted. Table 2 shows the daily requirements of niacin as recommended by the

22. Niacinamide was liberally supplied by Merck & Co., Inc., Rahway, N. J.

23. Butler, A. M.: Nutritional Requirements in Infancy and in Childhood, Am. J. Dis. Child. **64**:898 (Nov.) 1942.

Food and Nutrition Board of the National Research Council. If these figures are correct, it is necessary that a large amount of meat, whole grain cereals, fortified bread, legumes and banana be included in the diet to make up the minimum requirement.

According to these criteria, the diets of our patients were probably deficient. For 49 per cent the diets were grossly deficient. These children had meat only two or three times a week, one or two slices of bread a day, few vegetables and nuts, and legumes only rarely. The remainder had fair diets, as indicated by the inclusion of larger amounts of the aforementioned foods. All patients had 1 quart (1,000 cc.) of milk a day. Milk is a poor source of niacin. However, the diets of

TABLE 3.—*Distribution of Sixty Patients with Lesions of the Tongue Associated with Niacin Deficiency*

Age, Years	No. of Patients	Patients, %
Under 1	3	5.0
1 to 4	21	35.0
5 to 9	25	41.6
10 to 14	6	10.0
15 to 19	3	5.0
20 to 25	2	3.4
Total	60	100.0
Sex		
Boys	34	56.6
Girls	26	43.4
Total	60	100.0
Race		
White	49	81.5
Yellow	3	5.0
Negro	3	5.0
Puerto Rican	5	8.5
Total	60	100.0

the children with lesions of the tongue were fairly similar to those of the children with normal tongues.

The distribution of the 60 patients of this study according to age, sex and race is shown in table 3. All but 1 of the patients 18 years of age and over were mothers of newly born babies who were being studied; the 1 exception was an 18 year old youth with rheumatic fever. There were 26 girls and 34 boys. Of the children 3 were Negroes, 3 were Oriental and 5 were Puerto Ricans.

Socioeconomic Status.—A number of the children with glossitis migrans were seen in private practice. The other types of changes in the tongue were encountered only at Bellevue Hospital.

General Health.—The health of the children with glossitis migrans did not differ from that of the generality of children. This observation was true, also, of most of the children with swollen and with fissured

tongues, but several patients in these groups had a chronic disease, such as tuberculosis or rheumatic fever. In the sick children the appearance of the tongue varied with the course of illness and was unaffected by niacin therapy. In these patients the tongue to a considerable extent reflected an improvement in the disease state, the appearance improving as the illness improved and becoming worse as the general condition deteriorated.

Familial Incidence.—In 15 of the 60 patients, changes in the tongue were noted in a parent, a sibling or a grandparent. The lesions of the tongue in the various members of the family were not always of the same character. In several instances, a child with glossitis migrans had a parent with fissured tongue. In 1 instance, a mother, aged 34, and her 3 sons, aged 13, 12 and 10 years, respectively, when first observed showed similar changes in the tongue (figure, *5 a, b, c* and *d*). The tongues were large, and their surfaces were irregular. The fungiform papillae were large and pale and looked edematous. The general health

TABLE 4.—*Comparison of Results for Patients Treated with Niacin and for Untreated (Control) Patients*

	Condition of Tongue		Total Number
	Improved	Unimproved	
Untreated patients *	4	12	16
Treated patients	14	3	17

* Patients with glossitis migrans were excluded.

of the boys, judged by the usual criteria, was excellent, and their diets were better than average. Treatment with niacin was without effect.

RESULTS

Treatment was without effect in the 13 children with glossitis migrans. In 14 of the remaining 17 patients, some improvement took place (table 4). None was entirely cured, even though treatment of 2 patients was continued for twenty-four and twenty-six months, respectively. The average duration of niacinamide therapy was 15.5 months, and the average period of observation for the control group was 12.9 months. In no patient did improvement take place before treatment had been continued for three months.

In patients responding to therapy, there was a gradual replacement of the filiform papillae in the center of the tongue. This process progressed slowly toward the tip and the margins. At the same time the size of the tongue decreased, and the tooth indentations on the margins disappeared. Swelling and redness of the fungiform papillae diminished, and the matted filiform papillae, present on the posterior half or third of the tongue, became more discrete. In tongues with deep fissures

which had been devoid of papillae, the filiform papillae gradually filled the crypts of the fissures. The tip and the margins of the tongue were always the last areas to be covered with filiform papillae.

The tongue of a patient who responded favorably to niacinamide therapy is illustrated in 6 of the figure. This patient was a 14 year old boy with asthma of two years' duration. He received 100 mg. of niacinamide daily for twenty-two months, without change in the appearance of the tongue. The dose was then increased to 500 mg. daily. After three months, definite improvement was observable. The appearance of the tongue continued to improve for ten months, during which time large doses were given. It never became entirely normal.

Untreated Patients.—Excluding 14 patients with glossitis migrans from the untreated group, there remained 16 patients. Of these, the condition showed spontaneous improvement in 4 and remained unchanged in 12. Change, when it occurred, was similar in character and progress to that in the treated group.

COMMENT

The dramatic changes in the tongue which take place within a few days after treatment is instituted in patients with active pellagra were not observed in our patients. When improvement did occur, it was only after large doses of niacinamide had been administered for several months; and it was slow and irregular. In some instances there was no improvement, and it was not possible to predict which children would respond to treatment and which would not. Those with glossitis migrans did not respond to niacinamide therapy. It is unlikely, therefore, that the lesions of the tongue commonly observed in children are due to niacin deficiency.

A significantly larger number of children given prolonged niacinamide therapy showed improvement than did the children of an untreated (control) group. It seems reasonable to assume from this fact that niacin has a favorable influence on the nutrition of the tongue.

SUMMARY AND CONCLUSIONS

Lesions of the tongue are common in children.

Four types of lesions of the tongue were observed in the present series: acute glossitis; glossitis migrans, or geographic tongue; mild swelling of the tongue, and fissures of the tongue.

The effect of large doses of niacinamide (nicotinamide U. S. P.) (8 to 20 mg. per kilogram of body weight) on the lesions of the tongue of a group of children was studied and the results were compared with the results for an untreated group.

The acute glossitides improves spontaneously or after chemotherapy. They occurred secondary to a chronic lesion of the tongue.

Of the patients with swollen and fissured tongues who were treated with niacin (nicotinic acid U. S. P.) a larger proportion showed improvement (14 out of 17) than was observed among patients who received no therapy (4 out of 16).

In no patient was complete cure effected, although treatment was continued in 2 patients for as long as twenty-four and twenty-six months, respectively.

Glossitis migrans was unaffected by niacinamide therapy.

The diets of children with changes of the tongue were not demonstrably different from the diets of children without such changes.

These results lend support to the view that niacin has a favorable influence on the nutrition of the tongue. They fail to substantiate the view that the lesions of the tongue commonly seen in children are due to niacin deficiency.

132 East Seventy-First Street.

BASAL METABOLISM OF CHILDREN WITH TUMORS

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AFTER basal metabolic tests had been performed for 2 children admitted to the hospital with a diagnosis of tumor, it was noted that the child with a malignant neoplasm had a greatly increased basal metabolic rate while the child with a benign tumor had a normal rate. In order to determine whether this was an accidental observation or whether there is an association between malignancy and an elevated rate of metabolism, a review was made of the records of children previously admitted with a similar diagnosis.

The purpose of this paper is to report the results of this review. That the number of cases reported is small is explained partly by the fact that neoplasms in childhood are relatively infrequent compared with other causes for admission to the hospital and partly by the fact that infants and young children who could not cooperate in the metabolism tests necessarily had to be excluded. Then, too, only children with normal temperatures could be included in this report. The results, however, are interesting and perhaps significant.

There are 40 children included in this report. Of these, there were 21 children with tumors of the brain and 19 with tumors elsewhere in the body. The tests were made in duplicate under standard conditions, that is, in the postabsorptive state, with the children at rest. The Benedict-Roth apparatus was used. The tests were all made by me.

Table 1 gives the data for the 21 children with tumors of the brain and table 2 the data for the 19 children with tumors elsewhere in the body. The chart (fig. 1) represents graphically the percentage deviation from the normal zone of metabolism in each child. The standard used was one based on the sitting height, which is a linear surface, thus eliminating any possible error due to excessive weight deviation. This standard, first introduced by von Pirquet [1] has been repeatedly checked against the standard based on total height recommended by Talbot [2] and found to agree within 5 per cent.[3]

From the Pediatric Service of Dr. Murray H. Bass, Mount Sinai Hospital.

1. von Pirquet, C.: System der Ernährung, Berlin, Julius Springer, 1919.
2. Talbot, F. B.: Physiol. Rev. 5:477, 1925.

(Footnotes continued on page 672)

TABLE 1.—*Basal Metabolic Rate of Children with Tumor of the Brain*

Case Number	Sex	Age, Yr.	Height, Cm.	Sitting Height, Cm.	Weight, Kg.	Pulse, Beats per Min.	Basal Metabolism, Total Calories	Basal Metabolic Rate, %	Diagnosis and Comment
1	M	5	100	59	20	54	608	—13	Neuroblastoma of the inferior vermis
2	M	7	112	61	31	56	649	—13	Neuroblastoma
3	M	9	121	68	42	56	864	— 7	Pituitary adenoma; highly probable but not verified
4	M	11	150	80	43	52	1,123	—13	Spongioblastoma; craniotomy; improved
5	M	16	150	76	52	60	1,080	—11	Pituitary adenoma; highly probable but not verified at the time
6	M	18	151	76	61	56	1,029	—21	Pituitary adenoma; craniotomy; improved (this is case 5, two years later)
7	M	10	138	73	47	56	841	—21	Pituitary adenoma
8	M	9	136	72	17	56	887	—17	Glioma
9	M	6	117	62	20	60	726	— 9	Medulloblastoma
10	M	11	150	80	40	54	1,025	—20	Diffuse spongioblastoma; died
11	M	6	111	61	18	62	700	— 5	Cerebellar tumor; highly probable but not verified
12	F	9	134	72	19	60	1,007	— 3	Tumor of optic nerve and chiasm
13	F	10	136	72	19	60	934	—10	Glioma of right parietal region
14	F	11	140	73	32	54	886	—17	Cerebellar tumor
15	F	10	138	74	28	58	895	—20	Glioma
16	F	9	135	71	16	54	840	—17	Medulloblastoma
17	F	9	144	77	24	64	1,025	—14	Spongioblastoma
18	F	7	114	64	23	60	748	— 9	Rathke's pouch tumor
19	M	6	112	61	31	70	700	— 6	Pituitary adenoma
20	F	11	132	71	30	68	864	—14	Posterior fossa tumor
21	M	8	126	68	22	66	830	—11	Medulloblastoma

TABLE 2.—*Basal Metabolism of Children with Tumors Other Than in the Brain*

Case Number	Sex	Age, Yr.	Height, Cm.	Sitting Height, Cm.	Weight, Kg.	Pulse, Beats per Min.	Basal Metabolism, Total Calories	Basal Metabolic Rate, %	Diagnosis and Comment
1	F	5	110	60	16	90	972	+35	Neuroblastoma; thoracic ganglions; died
2	F	12	145	77	30	100	1,570	+31	Reticulum cell sarcoma; radiation therapy; basal metabolic rate fell to +2%; died
3	F	10	140	73	26	96	1,439	+35	Lymphosarcoma; after roentgen therapy basal metabolic rate fell to −2%; died
4	M	7	108	60	19	92	1,030	+50	Neuroblastoma; died
5	M	9	128	69	32	100	1,514	+59	Embryonal cell carcinoma; mediastinum; after roentgen therapy basal metabolic rate fell to +12%; died
6	M	8	127	69	24	120	1,330	+40	Lymphoblastoma; died
7	F	6	122	64	19	106	1,123	+38	Neuroblastoma (fig. 3); died
8	F	6	108	57	20	92	1,080	+41	Lymphosarcoma; after roentgen therapy basal metabolic rate fell to +18%; died
9	M	11	160	81	64	90	1,830	+40	Lymphosarcomatosis; all abdominal organs; died
10	F	9	128	69	30	98	1,237	+30	Lymphosarcomatosis; cervical glands and pelvis; died
11	M	5	114	62	19	80	1,076	+40	Neuroblastoma; biopsy; after roentgen therapy basal metabolic rate was +10%
12	M	8	133	62	23	100	1,289	+45	Lymphosarcoma; mediastinal nodes; died
13	F	11	143	75	30	92	1,325	+27	Reticulum cell sarcoma; died
14	M	4	107	55	18	90	855	+43	Mediastinal metastases of adenocarcinoma of testis removed at age 2; died
15	M	6	120	65	21	80	907	+ 9	Ganglioneuroma of posterior mediastinum; improved (figs. 2 and 4)
16	M	8	127	69	25	86	1,037	+ 9	Well encapsulated mediastinal teratoma; excision; improved
17	M	6	122	66	20	80	975	+12	Mediastinal neurofibroma; radiotherapy; improved for 5 years
		11	142	75	29	90	1,478	+31	Generalized neurofibromatosis; died
18	F	7	120	62	21	99	1,037	+30	Lymphosarcoma of maxilla with metastasis to lungs
19	F	12	142	76	34	98	1,560	+35	Reticulum cell sarcoma; after radiotherapy basal metabolic rate fell to +15%; died

In comparing the results in tables 1 and 2, one interesting fact stands out. All the children with tumors of the brain had a minus basal metabolic rate (column 9, table 1). In striking contrast, all the children with tumors situated elsewhere had a plus metabolic rate (column 9, table 2). Not only was the metabolic rate on the plus side, but except for the rate in 3 cases the metabolism was greatly elevated. This is more readily seen from the chart (fig. 1). In this chart the metabolic rate in all children with tumor of the brain (represented by a circle) can be seen to fall within the minus zone. There were 7 children with a metabolic rate between 0 and — 10 per cent and 14 with a metabolic rate below — 10 per cent. This group included children with the highly malignant neuroblastoma, medulloblastoma and spongioblastoma, as well as the more benign glioma, pituitary adenoma and craniopharyngioma. The diagnosis for all except 2 children of this group was verified by biopsy, craniotomy or autopsy. The 2 children in cases 3 and 11

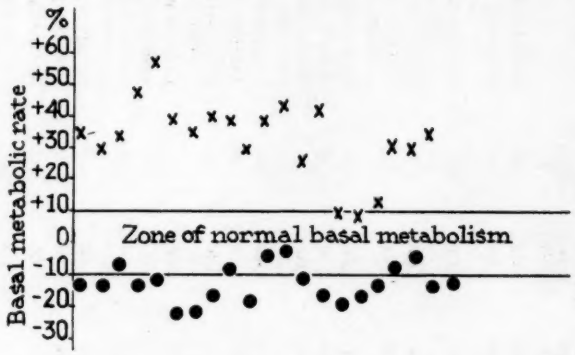

Fig. 1.—Chart showing basal metabolic rate of children with tumors. Circles (O) indicate tumor of the brain (21 cases). Crosses (×) indicate tumors elsewhere in the body (20 cases). Case 17 (table 2) is represented twice, once on each admission of the patient to the hospital.

(table 1) were the only ones for whom the diagnosis, although highly probable, was not actually verified, since they were lost sight of. Irrespective of whether the tumor of the brain was benign or malignant, all 21 children had a lowered basal metabolism.

On the other hand, the basal metabolic rate was increased in all the 19 children with tumors other than tumors of the brain. These

3. Topper, A., and Mulier, H.: Basal Metabolism of Children of Abnormal Body Weight: Basal Metabolism of Overweight Children, J.A.M.A. **92**:1903 (June 8) 1929; Basal Metabolism in Underweight Children, Am. J. Dis. Child. **38**:299 (Aug.) 1929. Topper, A.: Acta pædiat. **16**:189, 1933; Standards of Basal Metabolism for Children of Retarded Growth, Am. J. Dis. Child. **45**:1203 (June) 1933. Topper, A., and Mulier, H.: Basal Metabolism in Asthma and in Epilepsy, ibid. **46**:963 (Nov., pt. 1) 1933. Topper, A., and Rosenberg, H.: Basal Metabolism of Tuberculous Children, ibid. **52**:266 (Aug.) 1936.

are represented by crosses in the chart. From the chart it may be seen that 3 of these children had a normal metabolic rate, between 0 and + 12 per cent. All the rest, 16 children, had a greatly elevated metabolic rate ranging from + 27 per cent to + 50 per cent. The 3 children with normal metabolism had benign tumors. Case 15 (table 2) was that of a mediastinal ganglioneuroma. The basal metabolic rate in this case was + 9 per cent. Case 16 (table 2) was that of a well encapsulated mediastinal teratoma. In this case the metabolic rate was + 9 per cent. In both cases the tumor was removed, the children each making an uneventful recovery. Another child (case 17, table 2) had a mediastinal neurofibroma and a metabolic rate of + 12 per cent. Radiotherapy resulted in temporary improvement for five years.

Aside from these 3 children with benign tumors and normal basal metabolism, each of the other 16 children had a greatly increased metabolic rate. These 16 children all had highly malignant tumors, including neuroblastoma, sarcoma, lymphosarcoma, carcinoma and adenocarcinoma. In addition, it should be noted here that 1 child (case 17, table 2), five years after his first admission to the hospital, was readmitted with malignant degeneration of his originally benign tumor; his metabolic rate had increased to + 31 per cent. (In all the 19 children with tumors other than of the brain, the diagnosis was verified either by biopsy or operative or postmortem observation.)

This demonstration of an increased basal metabolic rate in all the children with malignant neoplasms was interesting, but needed to be explained. It is known that the basal metabolism may be increased by fever, by hyperactivity of the thyroid gland, in puberty and by certain blood dyscrasias. I could discover none of these causes in this series. The children were all afebrile. None of them manifested signs of hyperthyroidism. Puberty as a factor in the increase of metabolism could be excluded, since the ages of the children ranged from 4 to 12 years and the elevation in metabolic rate was observed irrespective of the age. Blood dyscrasias can likewise be excluded. How then can the increased rate of metabolism in all these children with malignant tumors be explained?

A vigorous search through the literature showed surprisingly few similar studies. Occasionally a brief reference could be found, as, for example, in a recent paper by Craver.[4] In his report on "Lymphomas and Leukemias" he stated, "The basal metabolic rate may be considerably elevated, not only in leukemia but in Hodgkin's disease and lymphosarcoma . . ."[5] Aside from this brief reference, I could discover no

4. Craver, L. F.: Bull. New York Acad. Med. **23**:79, 1947.

5. Although my records included many cases of leukemia and Hodgkin's disease, these have been excluded from the present report, since the inclusion of these two diseases in the neoplastic classification is still challenged.

reports of studies of basal metabolism in children with neoplasms and only a few meager reports of such studies in adults. Some authors, however, stress the enormously increased activity of malignant tissue, which may shed some light on the increased basal metabolic rate since the basal metabolism depends on the activity of protoplasmic tissue.

As early as 1889, Müller [6] studied the nitrogen metabolism of 5 adults with carcinoma in an attempt to explain their cachexia. He observed that the nitrogen excretion is greater than the nitrogen ingestion. Even with an ample intake of food, nitrogen equilibrium could not be attained. Similarly Lauter and Jenke [7] reported the minimum nitrogen excretion in patients with carcinoma to be 3.76 Gm., or twice the normal amount. This quantity was even greater than that of a patient with toxic diffuse goiter (Graves's disease), whose basal metabolic rate was + 85 per cent and whose nitrogen excretion was 2.15 Gm. In 1906 Magnus-Levy [8] stated that ". . . the heat production of patients with carcinoma may be increased 30 to 40 per cent above the normal despite the characteristic cachexia." Knipping,[9] in 1927, reported a case of lymphosarcoma in an adult with a "greatly increased metabolism" and postulated that some chemical substance thrown off by the tumor into the blood stream explained this increase. Schneider [10] in 1928 described 9 cases of malignant tumor in adults who had metabolic rates ranging from + 19 to + 35 per cent. He explained the increase on the basis of acidosis. In 1935, Jura [11] reported on a series of adults with malignant tumors. He observed an increased basal metabolic rate, which became lower after removal of the tumors. Jura stated that the increased metabolic rate may be due to glutathione, which he discovered in increased amounts in malignant tissue and which, according to the belief he expressed, acts as a catalyst of cellular activity; with the tumor removed, the stimulus to increased cellular activity is no longer present and the metabolic rate falls. This theory received some corroboration from the studies of Edebacher and Koller,[12] who produced experimental sarcoma in rats and noted a high content of glutathione in the sarcoma tissue of the rats. In analogous studies made in order to explain the rapid growth of malignant tissue, Novi [13] demonstrated an abundance of arginase and phosphotase in sarcoma tissue and suggested that their presence may be indicative of the cellular

6. Müller, F.: Ztschr. f. klin. Med. **14**:406, 1889.
7. Lauter, S., and Jenke, M.: Deutsches Arch. f. klin. Med. **139**:46, 1922.
8. Magnus-Levy, A.: Ztschr. f. klin. Med. **60**:177, 1906.
9. Knipping, H. W.: Ergebn. d. inn. Med. u. Kinderh. **31**:19, 1927.
10. Schneider, E.: Deutsche Ztschr. f. Chir. **211**:1, 1928.
11. Jura, V.: Riv. di pat. sper. **15**:35, 1935.
12. Edebacher, S., and Koller, F.: Ztschr. f. physiol. Chem. **227**:99, 1934.
13. Novi, M.: Clin. chir. **36**:629, 1933.

activity of rapidly growing tissue. Novi reported that the content of glutathione in sarcoma tissue was greater than that in connective tissue tumors. Since glutathione is a catalyzing agent, Novi suggested that this may account for the slower growth of benign tumors.

All these studies indicate that the cellular activity of malignant tissue is great. It was Warburg,[14] however, who shed the greatest light on the metabolism of tumor cells. From his comprehensive studies, it would seem logical to seek the explanation of the increased basal metabolic rate in the vigorous metabolism of tumor cells per se rather than in any extraneous stimulus. According to Warburg the metabolism of the malignant tumor cell is eighty times as vigorous as that of working muscle and two hundred times that of resting muscle. When one considers that resting muscle accounts for 40 per cent of the total metabolism and that muscular activity can increase the metabolic rate by as much as 200 per cent, one begins to appreciate the magnitude of the metabolism of malignant tissue. Glycolysis explains the increase in the metabolism of working muscle. The most pronounced characteristic of the metabolism of tumor cells is glycolysis, which results in the production of lactic acid. When lactic acid is formed, there is a concomitant rise in protein metabolism, which in turn increases the oxidative processes. Cori and Cori[15] observed that the excess of lactic acid produced by malignant tumors is eliminated into the blood stream.

Warburg's theory of the tremendous metabolism of tumor cells explains the rapid growth of malignant tumors, since "the energy liberated in the process of glycolysis is utilized in the case of muscle for activity and in the case of malignant tissue for growth and reproduction."[14] Warburg, and later Novi, discovered the glycolytic activity of benign tumor tissue to be much less than that of malignant tumor tissue. This may well explain the normal metabolic rate in the 3 children with benign tumors (cases 15, 16 and 17, table 2).

That the stimulation to increased metabolism in persons with malignant tumors is not due to increased activity of the thyroid gland can be deduced from the studies of many investigators. Meyer, McTiernan and Aub,[16] and later Meyer and McTiernan,[17] showed that while thyroxin elevates the metabolic rate of isolated tissue, as well as that of the intact organism, it has no effect on malignant tissue. While

14. Warburg, O.: Metabolism of Tumors, London, Constable & Co., Ltd., 1930.

15. Cori, C. F., and Cori, G. I.: Textbook of Biochemistry, Philadelphia, Harrow & Sherwin, 1935.

16 Meyer, O. O.; McTiernan, C., and Aub, J.: J. Clin. Investigation **12**: 723, 1933.

17. Meyer, O. O., and McTiernan, C.: Am. J. Cancer **20**:96, 1934.

theorizing about the high rate of metabolism of tumor cells, they asked, "Does the tumor cell represent a stage of life so elemental that it antedates the hormone?" Jura called attention to the fact that while the basal metabolic rate of patients with cancer remains elevated even as cachexia develops, the thyroid gland in these patients may become atrophied as a result of malnutrition. Lerman,[18] after reviewing the entire subject of the relationship between thyroid activity and malignancy, concluded that the "state of thyroid function is not important in experimental tumors."

Within recent years, there have been many studies of the level of iodine in the blood as an index of circulating thyroid hormone. Some investigators [19] are even of the opinion that the amount of iodine in the blood may be a more reliable criterion than the basal metabolic rate in the diagnosis of hyperthyroidism. The fact that normal levels of iodine in the blood have been observed in animals with experimental tumors and in patients with carcinoma [20] affords additional proof that the thyroid gland cannot be implicated in the increased metabolic rate accompanying malignancy.

From all these studies, it may be concluded that the stimulation to an increased rate of metabolism in children with malignant tumors is within the tumor itself. Additional corroboration is in the studies of Jura, who noted a lowering of the metabolic rate after excision of the tumor. Again, radiotherapy, with destruction of the tumor tissue, is followed by a lowering of the rate of metabolism.[21] This fact was also noted in the children of the present series who received roentgen therapy (cases 2, 3, 5, 8, 11 and 19, table 2).

Since the rate of basal metabolism is increased in persons with malignant tumors because of the activity of the tumor cells per se, the question arises as to why all tumors of the brain, even those highly malignant, are associated, not with an increased, but actually with a lowered basal metabolic rate.

Bradycardia is a common observation in persons with tumor of the brain. From table 1, column 7, it can be seen that all of the children

18. Lerman, J.: Surgery **16**:266, 1944.

19. Perkins, J. J., and Cattell, R. B.: West. J. Surg. **48**:50, 1940. Salter, W. T.: The Endocrine Function of Iodine, Boston, Harvard University Press, 1940. Salter, W. T., and Bassett, A. M.: Tr. A. Am. Physicians **56**:77, 1941. Riggs, D. S.; Gildea, E. F.; Man, E. B., and Peters, J. P.: J. Clin. Investigation **20**:345, 1941.

20. Curtis, G. M., and Fertman, M. B.: Blood Iodine Studies: Analysis of Blood Iodine in Thyroid Disease, Arch. Surg. **50**:207 (April) 1945.

21. Lennox, W. G., and Means, J. H.: A Study of the Basal and Nitrogenous Metabolism in a Case of Acute Leukemia During Roentgen Ray Treatment, Arch. Int. Med. **32**:705 (Nov.) 1923. Uhlman, E. M., and Goldner, M.: Radiology **42**: 165, 1944.

with tumor of the brain had a slow pulse rate, ranging from 52 to 70 per minute. In 1925, Schick and his co-workers [22] suggested that the bradycardia might be caused by a low basal metabolism, rather than by stimulation of the vagus nerve. Guillain and his co-workers [23] and Castex, Ontaneda and Schteingart [24] reported the observation of a lowered rate of metabolism in persons with tumor of the brain. Schick and Topper [25] also observed a lowered basal metabolic rate in 2 persons with tumor of the brain.

The fact that pituitary tumors are associated with a lowered basal metabolic rate is well known and can be explained on the basis of reduced hormone stimulation. In the present report the tumors of 6 of the children were in this category (cases 3, 5, 6, 7, 18 and 19, table 1). However, all the other children with tumors in other areas of the brain also had a lowered rate of metabolism, which probably could not be explained on the basis of lowered secretory activity of the pituitary gland. Most of these tumors were malignant, so that one would be led to expect an increased rate of metabolism on the basis of the increased activity of malignant tissue. One is left with the thought, then, that there may be some factor which counteracts the metabolic activity of malignant tissue in the brain. It is known, furthermore, that tumors of the brain, no matter how malignant, grow more slowly than malignant tumors elsewhere in the body. It is known, too, that tumors of the brain never metastasize. Other factors also come into play.

The plane of heat production is largely dependent on the skeletal muscles, which in turn are dependent on their connection with central nerve stimuli. If the connection is severed by curare or by section of the spinal cord or abolished by anesthesia, the metabolism falls to a low level. The brain produces nervous stimuli necessary for the irritability and activity of protoplasm. Pressure of the tumor may result in dulling of these nerve stimuli. Since the level of the total metabolism depends on cellular activity, any decrease in such stimuli would necessarily tend to lower the activity of the protoplasmic mass, with consequent lowering of the total rate of metabolism. Talbot,[26] in his study

22. Schick, B., and Cohen, P.: Lowered Basal Metabolism in Post-Infectious Stages and in Diseases Characterized by Slow Pulse Rate: Preliminary Report, Am. J. Dis. Child. **30**:291 (Sept.) 1925. Schick, B.; Cohen, P., and Beck, I.: Basal Metabolism After Pneumonia, ibid. **31**:228 (Feb.) 1926.

23. Guillain, G.; Laroche, G., and Alajouanine, T.: Compt. rend. Soc. de biol. **92**:574, 1925.

24. Castex, M. R.; Ontaneda, L. E., and Schteingart, M.: Compt. rend. Soc. de biol. **106**:392, 1931.

25. Schick, B., and Topper, A.: Lowered Basal Metabolism in Conditions Characterized by Slow Pulse Rate, Am. J. Dis. Child. **45**:760 (April) 1933.

26. Talbot, F. B.: Arch. Pediat. **32**:452, 1915.

of the basal metabolism of a child with congenital absence of the cerebral hemisphere, reported an extraordinarily low basal metabolic rate. Popow and Bajandurow [27] observed decreased metabolism in decerebrated birds. Evidently the removal of the normal influence of the cerebrum on cellular activity is followed by reduced visceral requirements for oxygen. The vital functions are carried on at a lowered plane, so to speak, with a reduced production of heat.

Aside from a hypometabolism on the basis of dulled stimuli of the central nervous system, a special pressure effect on the areas concerned with secretory regulation of metabolism may be further postulated. When the skull is thought of as a closed cavity, it is realized that tumors anywhere within this space may exert pressure on otherwise uninvolved parts of the pituitary structure, resulting in a hypopituitary syndrome of lowered metabolism. Or there may be pressure on the hypothalamus, with resulting disturbance of the pituitary gland and lowering of the metabolic rate. There is evidence that the hypothalamus may initiate impulses which act through the pituitary gland to control metabolism. Gräfe and Grünthal [28] and Andreu Urra [29] reported a fall in the basal metabolic rate after injection of silver nitrate into the caudal hypothalamus of dogs. Mazzoco [30] observed a drop in the basal metabolic rate to about 15 per cent below normal in dogs with lesions in the tuber cinereum. Bruhn [31] reported a metabolic rate of about 12 per cent below normal in a monkey with a damaged hypothalamus. According to one theory,[32] such a lowering of the basal metabolism is evidence of a disturbance in the hypothalamus-pituitary relation.

Whatever the mechanism, the fact remains that tumor of the brain is associated with a low rate of basal metaboiism. This low rate is seen whether the neoplasm is benign or malignant. In striking contrast, tumors elsewhere in the body, when malignant, cause a great increase in the basal metabolic rate. Benign tumors probably affect the metabolism insignificantly, if at all.

Aside from the general interest inherent in these observations, the question arises as to whether the basal metabolic test may be made to serve some practical clinical purpose. In disturbances of the thyroid the basal metabolic rate is an important aid in diagnosis. Can the basal metabolic rate be used also in the diagnosis of tumors?

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27. Popow, N. A., and Bajandurow, B. J.: Arch. f. d. ges. Physiol. **221**:412, 1929.

28. Gräfe, E., and Grünthal, E.: Klin. Wchnschr. **8**:1013, 1929.

29. Andreu Urra, J.: An. de med. int. **1**:945, 1932.

30. Mazzoco, P.: Rev. Soc. argent. de biol. **8**:621, 1932.

31. Bruhn, J. M.: Am. J. Physiol. **110**:477, 1934.

32. Karplus, J. P., and Peczenik, O.: Arch. f. d. ges. Physiol. **225**:654, 1930; **232**:402, 1933.

In adults the cardinal symptoms of headache, vomiting and disturbances in vision easily establish the diagnosis of tumor of the brain. In children, however, these symptoms are often absent or inconspicuous. The explanation for this lies in the fact that the sutures between the bones of the calvarium do not become firmly closed until near puberty. Before that period, therefore, any increase in tension can be reduced by separation of the sutures, producing a spontaneous decompression and thus relieving the symptoms of increased intracranial pressure. Any diagnostic aid in such cases should be welcomed. A lowered rate of basal metabolism in a child in whom a tumor is suspected can be such a diagnostic aid. The basal metabolism of active growing normal

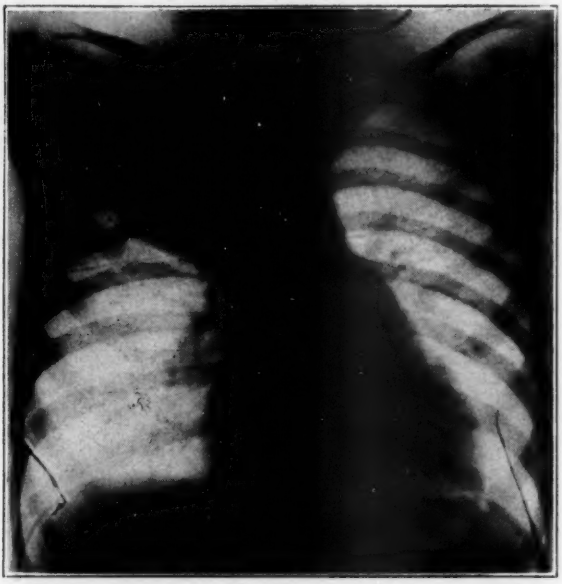

Fig. 2.—Roentgenogram of the chest of a child (case 15, table 2) with mediastinal ganglioneuroma and normal metabolic rate.

children is usually on a higher level than that of adults. In the absence of malnutrition or hypothyroidism, a metabolic rate in the minus zone of metabolism in a child, especially when associated with unexplained headaches or vomiting, should always lead one to suspect the presence of a tumor of the brain.

That the basal metabolic rate may also aid in the diagnosis of malignant tumors other than tumors of the brain is shown by the roentgenograms herein reproduced. Figure 2 is the roentgenogram of a child with a tumor of the mediastinum, whose basal metabolic rate was + 9 per cent (case 15, table 2). Figure 3 is the roentgenogram of a child with a mediastinal tumor, whose basal metabolic rate was + 38

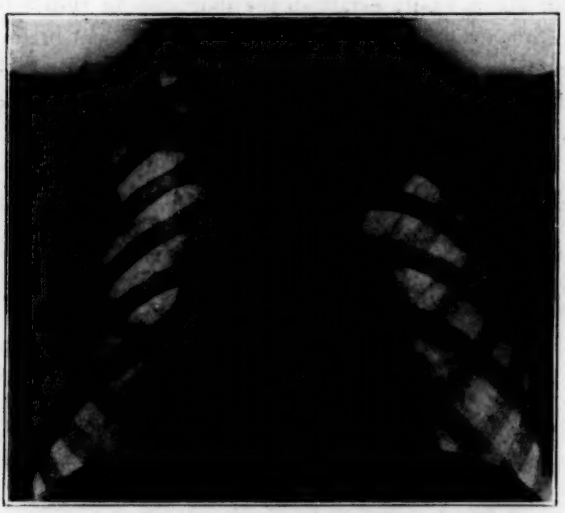

Fig. 3.—Roentgenogram of the chest of a child (case 7, table 2) with mediastinal tumor and elevated basal metabolic rate. The tumor proved to be a neuroblastoma on postmortem examination.

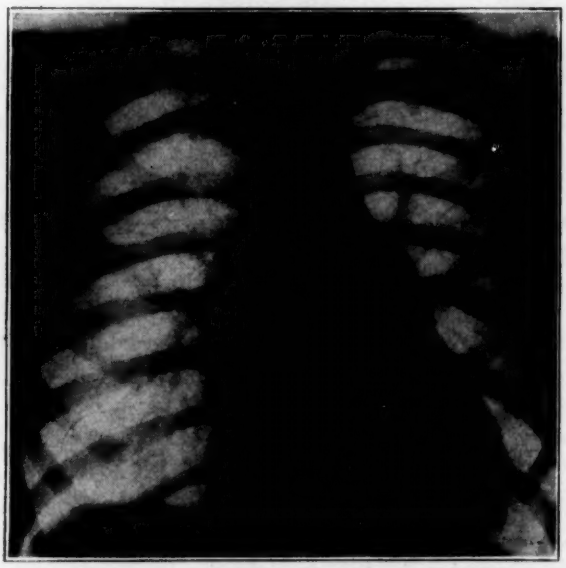

Fig. 4.—Roentgenogram of the chest of a child (case 15; see fig. 2) made four years after thoracotomy with removal of the tumor and subsequent recovery.

per cent (case 7, table 2). When the question arose as to the nature of the two tumors, the elevated rate of basal metabolism in case 7 led me to suspect malignancy. A roentgenogram of the long bones, made subsequently, showed metastases. The child died, and the postmortem examination revealed neuroblastoma. In the first child (case 15), whose basal metabolic rate was normal, biopsy of the tumor mass revealed a ganglioneuroma. Thoracotomy was performed, with removal of the tumor, and the child recovered completely. The roentgenogram in figure 4 shows this child's chest to be entirely normal four years later.

SUMMARY

Data are presented showing that the basal metabolic rates of children with tumors of the brain are lowered, irrespective of the character of the tumor. In contrast, children with malignant tumors other than of the brain have an elevated basal metabolic rate.

An attempt is made to explain these changes in metabolism.

It is suggested that the basal metabolic test may be of diagnostic aid in children in whom the presence of a tumor is suspected.

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HYPEROSMOLARITY AND HYPERELECTROLYTEMIA IN PATHOLOGIC CONDITIONS OF CHILDHOOD

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THIS report deals with the elevations in electrolyte content and osmolarity of the plasma that have been observed in the last two years in patients at the Cincinnati Children's Hospital. Its purpose is to draw attention to the frequent occurrence of hyperelectrolytemia in pathologic conditions of childhood, to outline some of the factors leading to hyperosmolarity of the body fluids and to present some conclusions with regard to the fluid management of patients exhibiting such derangements.

The validity of the dictum of Claude Bernard, that constancy of the internal milieu constitutes the condition of freedom for the cells of the body, has been amply established in the last forty years. With respect to the electrolytes of the body, the studies of Gamble [1] provided the outstanding contribution to this concept. He demonstrated the tendency of the electrolytes of the body fluids to remain constant in various experimental and clinical conditions and elucidated in detailed analyses the mechanisms by which such constancy of composition is achieved. He showed that the qualitative composition of the body fluids is safeguarded at the expense of changes in their volume. The total osmolarity and the electrolyte content are among the most jealously guarded properties; they appear to be more closely maintained than is the concentration of any single constituent of the plasma. Many of the deviations in the concentration of individual ions could be explained as compensatory changes to maintain the constancy of the osmolarity of the body fluids. These concepts have had not only theoretic but also great practical significance; they represent the theory underlying the modern fluid management of patients.

Deviations from the usual in the responses of the body that result in alterations of the osmolarity of the body fluids have been observed clinically and produced experimentally. Such observations, although in no way affecting the general validity of the basic concepts, outlined

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1. Gamble, J. L.: Chemical Anatomy, Physiology and Pathology of Extracellular Fluid: A Lecture Syllabus, Cambridge, Mass., Harvard University Press, 1942.

previously, have great clinical importance in the management of the fluid requirements of patients in whom such derangements develop. They are also of theoretic interest in permitting a clearer insight into the mechanisms of osmoregulation of the body.

Compared with the many clinical studies of *hypo*electrolytemia, there are few reports of the occurrence of *hyper*electrolytemia in pathologic conditions. The earliest reference is in the work of the father of electrolyte chemistry, Schmidt,[2] on the composition of blood and tissues of patients with cholera. The occurrence of increased electrolyte and solute concentrations in the plasma of infants with diarrhea was stressed by Salge.[3] Hamilton and his associates [4] in a study on 25 infants with acute diarrhea observed hyperelectrolytemia in 6, as compared with 14 of decreased content of electrolyte. Hyperelectrolytemia was also suggested in the report of Maizels and McArthur [5] and Phélizot.[6] More recently Kerpel-Fronius [7] drew particular attention to the occurrence of "dehydration because of loss of water" with retention and increased concentration of electrolytes in the body fluids, as contrasted to the more familiar "dehydration because of loss of salt," and reported on several infants with infection who exhibited hyperelectrolytemia.

Experimentally, hyperelectrolytemia has been produced in a variety of ways. Insufficient intake of water, particularly when combined with a normal caloric and protein intake, has been the most commonly employed procedure.[8] Withdrawal of food and water for extended

2. Schmidt, K.: Characteristik der epidemischen Cholera gegenüber verwandten Transudationsanomalien, Leipzig, G. A. Reyer, 1850.

3. Salge, B.: Die physikalischen Erscheinungen des Blutes beim gesunden und kranken Säugling: Der osmotische Druck, Ztschr. f. Kinderh. **1**:126, 1911.

4. Hamilton, B.; Kajdi, L., and Meeker, D.: Acidosis of Acute Diarrhea in Infancy, Am. J. Dis. Child. **38**:314 (Aug.) 1929.

5. Maizels, M., and McArthur, C. B.: Alkalaemia in the Diarrhea of Infants, Quart. J. Med. **23**:171, 1930.

6. Phélizot, G.: Le chlore, l'urée, la réserve alcaline, dans les déshydrations du nourisson: Déductions thérapeutiques, Rev. franç. de pediat. **7**:560, 1931.

7. Kerpel-Fronius, E.: Ueber die Wechselbeziehungen zwischen Kochsalz und Reststickstoff, Ztschr. f. d. ges. exper. Med. **85**:235, 1932; Theoretische und praktische Bemerkungen zur Flüssigkeitsbehandlung von Exsiccationszuständen, Monatschr. f. Kinderh. **81**:294, 1940.

8. (*a*) Hamilton, Kajdi and Meeker.[4] Maizels and McArthur.[5] Phélizot.[6] (*b*) Kerpel-Fronius, E., and Leövey, F.: Ueber die Stoerung der Osmoregulation bei der experimentellen Exsikkose, Arch. f. Kinderh. **94**:9, 1931. Csapo, J., and Kerpel-Fronius, E.: Zur Pathologie der Säuglingstoxikose: Ueber das Saeure-Basen-Gleichgewicht bei experimentellen Exsiccose, Monatschr. f. Kinderh. **58**:1, 1933. Schoenthal, L.: Acid Base Metabolism: Effects of Administration of Salt and of Restriction of Water, Am. J. Dis. Child. **37**:244 (Feb.) 1929. Hamilton, B., and Schwartz, R.: The Composition of Tissues in Dehydration, J. Biol. Chem. **109**:745, 1935. Danowski, T. S.; Elkinton, J. R., and Winkler, A. W.: The Deleterious Effect in Dogs of a Dry Protein Ration, J. Clin. Investigation **23**:816, 1944.

periods of time[9] or of water alone[10] may likewise produce such a condition. Injection of hypertonic salt solutions[11] or of urea[10] may also produce hyperelectrolytemia. Under the experimental conditions the concentration of total cations in the plasma may rise to values of 200 milliequivalents per liter and the osmolarity to 500 milliosmols per liter,[8b] levels 30 and 50 per cent above the normal. The studies have indicated that the changes in electrolyte concentration and osmolarity are not confined to the plasma or to the extracellular fluid alone, as seemed unlikely a priori, but are shared by the intracellular fluid as well.[12]

The occurrence of hyperelectrolytemia has been explained on the assumption that there exists an absolute upper limit of osmolarity of urine, beyond which the kidney cannot concentrate; this limit appears to be about 1,400 milliosmols per liter in adults,[13] but is considerably lower in infants.[12] Under conditions of lack of water, with both nitrogenous and electrolyte solutes claiming excretion by the kidney, retention of electrolytes ensues. The less the ability of the kidney to excrete urine of high solute content, the more readily hyperosmolarity of the body fluids develops. In infants the low limit of the solute content of the urine and the decrease in the limit with lowering of the rate of excretion of urine favor the occurrence of hyperosmolarity.[14a]

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9. Elkinton, J. R., and Taffel, M.: Prolonged Water Deprivation in the Dog, J. Clin. Investigation **21**:787, 1942.

10. Kerpel-Fronius, E.: Ueber die Beziehungen zwischen Salz-und Wasserhaushalt bei experimentellen Wasserverlusten, Ztschr. f. Kinderh. **57**:489, 1935. McCance, R. A.; Young, W. F., and Black, D. A. K.: The Secretion of Urine During Dehydration and Rehydration, J. Physiol. **102**:415, 1944.

11. Winkler, A. W.; Elkinton, J. R.; Hopper, J., Jr., and Hoff, H. E.: Experimental Hypertonicity: Alterations in the Distribution of Body Water, and the Cause of Death, J. Clin. Investigation **23**:103, 1944. Kirsner, J. B.: The Serum Electrolytes in the Dog Before and During Acute Alkalosis Induced by Sodium Bicarbonate, J. Biol. Chem. **145**:219, 1942.

12. Phélizot.[6] Elkinton, J. R., and Winkler, A. W.: Transfers of Intracellular Potassium in Experimental Dehydration, J. Clin. Investigation **23**:93, 1944.

13. Smith, H. W.: The Physiology of the Kidney, New York, Oxford University Press, 1937. Gamble, J. L.: The Water Requirements of Castaways, Proc. Am. Philos. Soc. **88**:151, 1944. McCance, R. A.: The Excretion of Urea, Salts and Water During Periods of Hydropaenia in Man, J. Physiol. **104**:196, 1945. Hervey, G. R.; McCance, R. A., and Tayler, R. G. O.: Forced Diuresis During Hydropenia, Nature, London **157**:338, 1946.

14. (*a*) Young, W. F.; Hallum, J. L., and McCance, R. A.: The Secretion of Urine by Premature Infants, Arch. Dis. Childhood **16**:243, 1941. McCance, R. A., and Young, W. F.: The Secretion of Urine by Newborn Infants, J. Physiol. **99**: 265, 1941. Young, W. F., and McCance, R. A.: Secretion of Urine by Dehydrated and Normal Infants, Arch. Dis. Childhood **17**:65, 1942. (*b*) Heller, H.: The Renal Function of Newborn Infants, J. Physiol. **102**:429, 1944.

METHODS

The methods used in the laboratory of the Children's Hospital Research Foundation, except for determination of osmolarity of plasma, were described elsewhere.[15] Osmolarity was estimated by the method of Barger (also White and Walker[16]) as follows: Into a capillary tube about 100 mm. long and 0.1 to 0.3 mm. in diameter were drawn 4 droplets 2 to 5 mm. in length of the unknown plasma alternately with 3 droplets of equal size of a standard solution of sodium chloride, a total of 7 droplets. The capillary tube was then sealed at both ends by drawing to a fine point. The length of all droplets was determined with a measuring microscope with an accuracy of plus or minus 0.01 mm. The capillary tube was then placed in an incubator at 37 C. After a period of twenty-four hours the changes in the size of all droplets were determined and averaged. An increase in the length of the plasma droplets indicated that the plasma was hypertonic with respect to the standard solution of sodium chloride, while the converse conclusion was justified if the length of the plasma droplets had decreased. In case of doubt the measurements were repeated after forty-eight to seventy-two hours. In all cases several capillary tubes with different concentrations of the solution of sodium chloride, estimated to cover the expected range of tonicity, were set up at one time. The solution of sodium chloride used was spaced in intervals of 0.01 molarity, and observations between two standards were estimated to 0.002 molarity. A source of error in the method, recognized but uncorrected, arose from the variable loss of carbon dioxide under the circumstances of the test. This resulted in an underestimate of the molarity of the plasma, which probably did not exceed 10 milliosmols, that is, about 3 per cent of the normal value.

MODE OF PRESENTATION

The data are presented in the form of diagrams, in the manner of Gamble. Two scales are plotted on the ordinate, the outer representing milliequivalents and the inner, twice in numerical value, representing milliosmols. Two interrupted lines indicating normal values for the osmolarity and electrolyte content of the plasma are drawn across the figures for easy reference. The actually determined value for the

15. Rapoport, S., and Guest, G. M.: The Effect of Salicylates on the Electrolyte Structure of the Blood Plasma: I. Respiratory Alkalosis in Monkeys and Dogs After Sodium and Methyl Salicylate; The Influence of Hypnotic Drugs and of Sodium Bicarbonate on Salicylate Poisoning, J. Clin. Investigation **24**:759, 1945.

16. White, H. L.: Observations on Intracapsular Pressure and Molecular Concentration of Renal Capsular Fluid in Necturus, Am. J. Physiol. **85**:191, 1928. Walker, A. M.: Comparisons of Total Molecular Concentration of Glomerular Urine and Blood Plasma from the Frog and from Necturus, J. Biol. Chem. **87**:499, 1930.

osmolarity is indicated by a solid line on top of the columns and the one calculated from the individual constitutents, where it differs from the determined value, by an interrupted line. The use of concentrations per unit of serum, instead of serum-water, introduces a systematic error which affects comparisons only when extreme changes in the protein content occur. Another inconsistency is introduced by portraying both the equivalencies and the osmolarities of the plasma constituents on the same ordinate. This discrepancy is greatest for the proteins, which because of their molecular weight do not significantly contribute to the osmolarity, but are of importance in the ionic balance. Their equivalency was calculated according to the formula of Van Slyke and his associates.[17] A constant equivalency of 1.6 per milliosmol was assumed for the inorganic phosphorus, regardless of the actual p_H of the plasma. This simplification introduced only an insignificant error. For the magnesium a constant value of 3 milliequivalents per liter was assumed and for the potassium, unless actually determined, a value of 5. A fraction designated as undetermined anions has been entered in most of the diagrams in order to even the cation and anion columns. It includes the proteins in the instances in which they were not determined. The osmotic equivalency of the nonprotein nitrogen was calculated on the assumption that it consisted entirely of urea.

OBSERVATIONS

In figures 1 to 5 are portrayed and in the table are summarized 14 cases of hyperelectrolytemia and increased osmolarity. The patients on whom the analyses were performed ranged in age from a few days to 12 years; most of them were infants. The nature of their illnesses was variable and will be mentioned in the course of the description of the chemical data.

In figure 1 are presented data illustrating elevation of electrolyte and osmotic concentrations in the plasma of 3 infants with diarrhea and fever and the results of treatment.

REPORT OF CASES

CASE 1.—M. Ha., a 9 month old infant, was admitted to the hospital on March 6, 1945, with a history of diarrhea, vomiting and fever of three days' duration. The examination revealed a poorly nourished and poorly developed child with severe dehydration. The abdomen was scaphoid. The temperature was 103 F. and rose to 106 F. in the first hours after admission. The composition of her plasma on admission is portrayed in the first diagram of figure 1. In the first eighteen hours 200 cc. of 5 per cent dextrose in isotonic solution of sodium chloride and 900 cc. of 5 per cent dextrose in water were administered by intravenous

17. Van Slyke, D. D.; Hastings, A. B.; Hiller, A., and Sendroy, J., Jr.: Studies of Gas and Electrolyte Equilibria in Blood: XIV. The Amounts of Alkali Bound in Serum Albumin and Globulin, J. Biol. Chem. **79**:769, 1928.

clysis. Transient hypocalcemia and convulsions developed, for which the patient was treated with calcium chloride. Her further course in the hospital was uneventful, and she was discharged well.

CASE 2.—N. Wu., a 12 month old girl, was admitted to the hospital on Aug. 21, 1945, with a history of diarrhea of two weeks' duration. Two days before admission temperature of 102 F. developed. She appeared somewhat improved on the day of admission, but the temperature suddenly rose to 106 F. Examination revealed a well developed fairly well nourished infant who appeared acutely ill. She was extremely lethargic and moderately dehydrated; the skin was pale and hot and the eyes dull and sunken. In the initial sample of blood the values depicted in the third diagram of figure 1 were observed. In the first twenty-four hours the child took 300 cc. of 5 per cent dextrose in water by mouth and received subcutaneously 200 cc. of 5 per cent dextrose in isotonic solution of sodium chloride

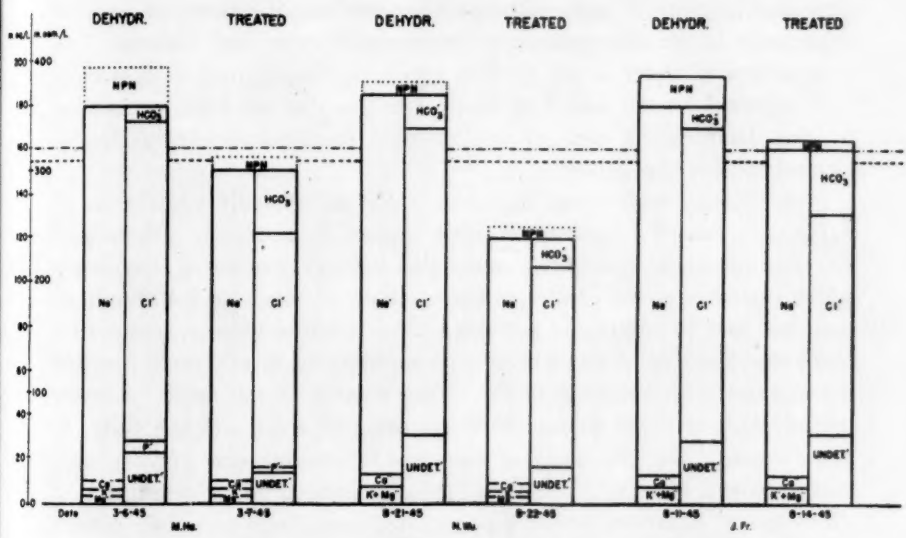

Fig. 1.—Shifts in electrolyte content and osmolarity of plasma of infants with diarrhea.

– . – . – . – normal electrolyte concentrations
– – – – – – – – – normal osmotic concentrations
. . . . . calculated osmolarity

and 500 cc. of 5 per cent dextrose in water. Treatment with sulfadiazine was also instituted. The fever and diarrhea subsided, and the patient improved.

CASE 3.—J. Fr., a 1 month old infant, was admitted to the hospital with a history of many liquid stools for one day. On admission the child weighed about 9 pounds (4,082 Gm.) and appeared acutely ill and dehydrated. The temperature was 102.5 F. The sample of blood, the data on which are depicted in the fifth diagram of figure 1, was taken at that time. The acidosis was corrected by administration of sodium bicarbonate, and continuous intravenous clysis was established. In thirty-six hours the patient received 350 cc. of 5 per cent dextrose in isotonic solution of sodium chloride and 700 cc. of 5 per cent dextrose in water. After two days, he began to take feedings well and the diarrhea ceased.

It may be seen from the figure that in each child the increased tonicity of the plasma, which exceeded normal by more than 20 per cent in patient M. Ha., was accounted for by the increases in the two principal extracellular ions, namely, sodium and chloride. The nonprotein nitrogen was variably affected, being decidedly elevated in patient M. Ha. and little changed in N. Wu. Other constituents of the plasma were not changed in an important manner.

Clinically, all 3 patients presented a picture of extreme dehydration. A noteworthy feature was a thick plastic putty-like consistency of the skin and the underlying tissues. The course of the diarrheal disease in all 3 was characterized by high temperature, which reached 106 F. in N. Wu. and M. Ha. There is little doubt that the fever, with the attendant increase in insensible loss of water, was the factor of greatest importance in the development of hyperosmolarity in their plasma. The expenditure of water in the form of vapor, unaccompanied with electrolyte, outweighed the losses of electrolyte via the intestine, occasioned by the diarrhea, as well as the possible compensatory excretion of electrolytes via the kidney.

Interference with renal function, while undoubtedly present in all 3 patients, varied considerably with respect to retention of nitrogen. In conditions of hydropenia with the kidneys exercising maximum water economy, urine of high solute content, as much as 1,400 milliosmols per liter in adults and perhaps half as much in infants, is excreted. With development of oliguria under conditions of stress, renal function deteriorates with lowering of the solute content of the urine. Greater urinary loss of water or increased retention of solutes in the body, or both, ensue. On the basis of such considerations one may surmise that in patient M. Ha., who showed greatly elevated nonprotein nitrogen, the stage of depressed renal function had been reached, while patient N. Wu. was in an earlier stage of hydropenia.

The result of treatment, also portrayed in figure 1, in each case was a reduction of the osmotic and electrolyte concentration. In M. Ha. the total osmotic concentration fell to a value slightly below normal and to a definitely subnormal level in N. Wu. This reaction of recovery, also seen in other patients with hyperelectrolytemia, suggests that renal function, perhaps more specifically the tubular function concerned with excretion of sodium and chloride ions, had been sufficiently affected to impair the ability of the kidneys to maintain the normal electrolyte concentration of the body fluids.

In figure 2 are shown 3 examples of the effects of diarrhea in young and small infants.

CASE 4.—Dav. G., one of triplets, was born prematurely after seven months of gestation, weighing 3 pounds 2 ounces (1,417.5 Gm.). At the age of 7 weeks when he weighed 5 pounds (2,268 Gm.), diarrhea developed, and he began to refuse

about a third of his formula. He became extremely dehydrated and lethargic. The sample of blood represented in the figure was drawn at that time. Oral feedings were discontinued and 180 cc. of 5 per cent dextrose in isotonic solution of sodium chloride and 160 cc. of 5 per cent dextrose in water were administered subcutaneously. The blood sample, the data from which are shown in the second diagram of figure 2, was obtained after this treatment. After several recurrences which required continuous intravenous clysis, the diarrhea subsided.

CASE 5.—Dan. G., a sibling of the patient just described, weighed 2 pounds 13 ounces (1,276 Gm.) at birth. The course of his illness was entirely like that of his brother and need not be detailed.

CASE 6.—W. Me., a 3 week old infant, was admitted to the hospital on Nov. 23, 1945. At the age of 2 days pronounced jaundice developed, the cause of which was determined to be erythroblastosis fetalis. He then began to have diarrhea, which became increasingly severe during the following two weeks. On admission he appeared severely dehydrated, malnourished and still slightly jaundiced. The skin

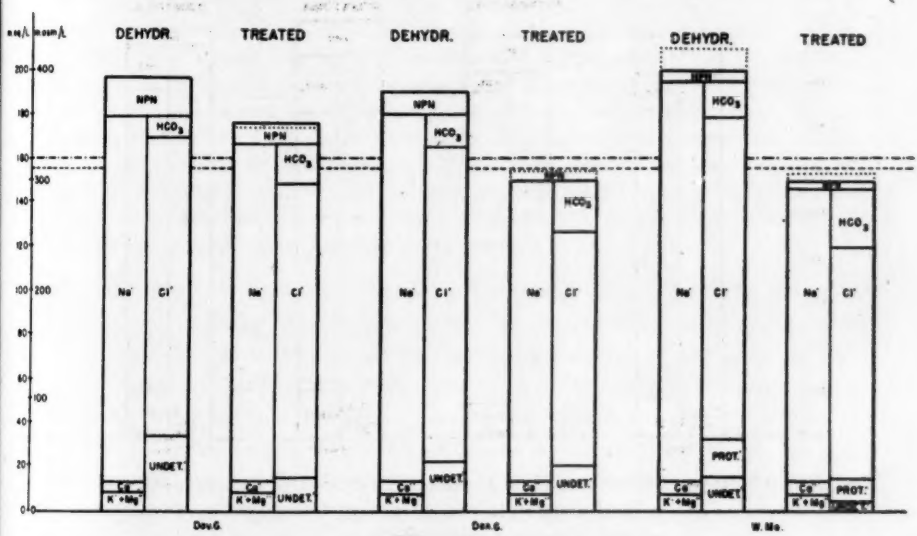

Fig. 2.—Hyperelectrolytemia and hyperosmolarity in young infants with diarrhea.
– . – . – . – normal electrolyte concentrations
- - - - - - - - - normal osmotic concentrations
. . . . . calculated osmolarity

and subcutaneous tissues appeared to be of thick putty-like consistency. The temperature was 99 F. The composition of the plasma on admission is portrayed in the third diagram of figure 2. Since the hemoglobin was 3.5 Gm. per hundred cubic centimeters, a blood transfusion was immediately administered. The patient was given continuous intravenous clysis, consisting mainly of 5 per cent solution of dextrose, and made a rapid uneventful recovery.

As may be seen from figure 2, all 3 infants had moderate hyperosmolarity of their plasma at the time of their dehydration. The increased tonicity was for the most part due to the increased concen-

tration of sodium and chloride, with retention of nitrogen contributing a significant share. All 3 patients had greatly reduced concentrations of bicarbonate, indicative of their acidosis. Appropriate treatment in all brought the composition of the plasma back to normal.

In these 3 infants two factors appear mainly responsible for the hyperelectrolytemia and hyperosmolarity in the face of electrolyte losses with the diarrheal stools: One, the more important, is the great insensibile expenditure of water in small and young infants. The second factor is the inability of the kidneys of small infants to excrete urine of high solute content.[14] One may infer that young and small infants require large amounts of water and that their treatment should include

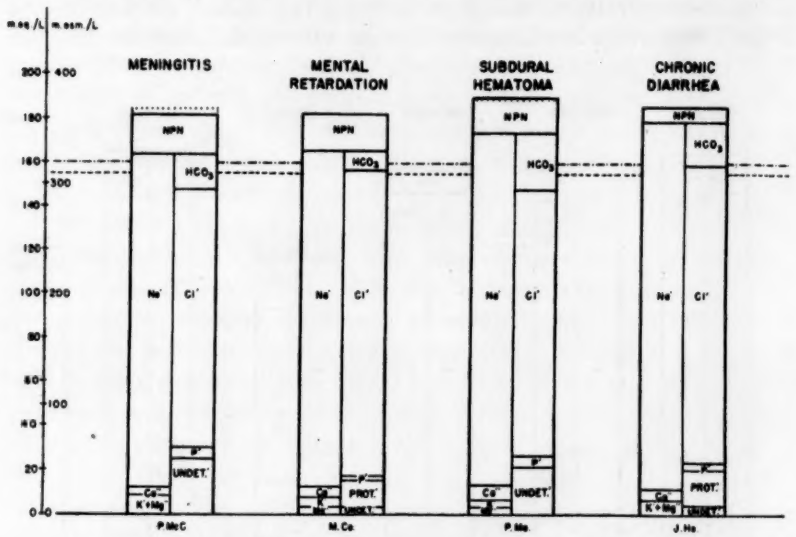

Fig. 3.—Hyperelectrolytemia and hyperosmolarity due to various causes.
– . – . – . – normal electrolyte concentrations
– – – – – – – – – normal osmotic concentrations
. . . . . calculated osmolarity

a greater share of electrolyte-free fluid if the structure of their plasma is to be preserved.

In figure 3 are shown 4 instances of hyperelectrolytemia observed in patients suffering from a variety of diseases.

CASE 7.—P. McC., an 8 month old infant, was admitted to the hospital with a history of fever and drowsiness of four days' duration. On the morning of admission convulsions developed. Physical examination revealed a comatose extremely dehydrated infant who appeared well nourished and developed. The skin was thick and rubbery in consistency. The temperature was 106.5 F. The composition of the plasma at that time is depicted in diagram 1 of figure 3. Examination of the spinal fluid revealed cloudiness and Hemophilus influenzae. The patient was given continuous intravenous clysis, consisting mainly of 5 per cent dextrose in water,

and treatment with sulfonamide compounds and specific antiserum was begun. His condition remained critical for twenty-four hours, but the further course was one of improvement to complete recovery.

As may be seen, the patient, when admitted exhibited an elevation in both electrolyte and nonprotein nitrogen content of the body fluids. For the most part, the disturbance was referable to the fever and the lack of fluid intake preceding his admission. Increased destruction of body protein caused by the infection may have been a factor contributing to the load imposed on his kidneys. The data on a small sample of urine obtained on admission, which showed a chloride concentration of 5.6 milliequivalents per liter and a nitrogen content of 738 mg. per hundred cubic centimeters, indicated the degree of impairment of renal function, which had depressed the ability of the kidneys to excrete urine of high solute content.

CASE 8.—M. Co., a 12 month old infant, was admitted to the hospital on Oct. 8, 1945. She had had four previous admissions for diarrhea and vomiting and had gained weight slowly. Examination revealed a small poorly nourished infant, only moderately dehydrated, who appeared mentally severely retarded and spastic. During the first ten days in the hospital the diarrhea was only moderate, and she was maintained on formula feedings. On the tenth day she was discovered to be severely dehydrated, and her skin assumed a plastic consistency. The composition of the plasma at that time is depicted in diagram 2 of figure 3. Convulsions and irregular respirations developed, and she died two days later.

The chemical data represented in diagram 2 of figure 3 were obtained during an episode of diarrhea which led to considerable dehydration. They indicate considerable elevation of the tonicity of the plasma, due to increase of electrolytes and retention of nonprotein nitrogen, and acidosis with considerable reduction of the carbon dioxide content.

In this patient the elevation of the concentration of solutes in the plasma was caused for the most part by insufficient intake of fluids. A contributory cause may have been in the spasticity and convulsions with attendant increase of heat production and of insensible expenditure of water. The severe diarrhea, by causing great losses of water and electrolyte, and the acidosis impaired further the status of the body fluids of the patient.

CASE 9.—P. Ma., a 4 month old infant, was admitted to the hospital with enlargement of the head. On examination the left side of his head appeared greatly enlarged. Extreme rigidity and a constant coarse tremor of both arms were present. Further studies and surgical intervention established the diagnosis of a left-sided subdural hematoma. During his stay in the hospital the temperature ranged between 100 and 102 F. He never took all feedings. Rigidity of musculature and tremors persisted. The analysis of many samples of plasma gave results similar to those depicted in figure 3.

In this patient insufficient intake of fluid and continuous muscular activity were the primary factors causing a state of hydropenia. The

fever, arising under these conditions, rendered more precarious the condition of water metabolism by increasing the expenditure of water.

CASE 10.—J. He., a 10 month old infant, was admitted to the hospital on Oct. 9, 1945. One month before admission an episode of diarrhea lasting one week occurred. Moderate diarrhea recurred, and some vomiting developed. On examination he appeared poorly nourished, chronically ill and moderately dehydrated. The skin was brownish, as is often observed in chronically ill infants. A loose cough was noted. During a five weeks' stay in the hospital the diarrhea was not so pronounced as were the cough and the persistent vomiting of the feedings. A variable elevation in temperature was present at all times, for which no adequate cause except dehydration was ever determined. When the chemical data set forth

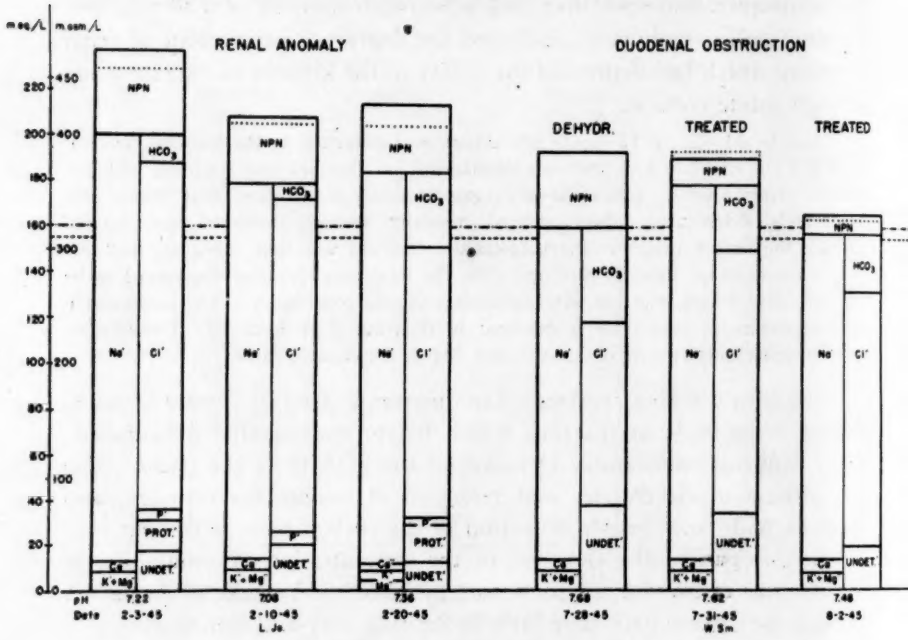

Fig. 4.—Diagrams showing the extent of hyperelectrolytemia in 2 children.
– . – . – . – normal electrolyte concentrations
- - - - - - - - - normal osmotic concentrations
. . . . . calculated osmolarity

in the fourth diagram of figure 3 were obtained, which showed decided increase of both electrolytes and nonprotein nitrogen, 900 cc. of 5 per cent dextrose solution were administered on each of two days. The fever promptly subsided; the composition of the plasma returned to normal, and striking improvement of the clinical condition took place.

This case illustrates a vicious cycle which may arise in a chronically ill infant. Whatever the original cause for failure of intake of sufficient fluid, this circumstance in itself appears to have been responsible for fever, which in turn caused greater expenditure of water.

The data on patient L. Jo., shown in the first three diagrams of figure 4, exemplify the occurrence of hyperelectrolytemia on the basis of a renal anomaly.

CASE 11.—L. Jo., a 6 week old infant, was admitted to the hospital on Jan. 8, 1945 for orthopedic repair of clubfoot (bilateral). On physical examination it was noted that the child had six toes on the right foot. In the hospital diarrhea developed. Nevertheless corrective plaster casts were applied. Following this procedure, the diarrhea increased greatly in severity, and dehydration with acidosis and nitrogen retention developed. Because of the critical condition of the patient the casts were removed, and a continuous intravenous clysis was started. The acidosis was corrected by the administration of sodium bicarbonate. However, the diarrhea and a tendency to acidosis persisted. After a second administration of sodium bicarbonate, hypocalcemia with convulsions developed. At that time it was noted that the child exhibited persistent nystagmoid movements of the eyes. Although the diarrhea diminished, the tendency to acidosis and the increase of nonprotein nitrogen remained. No further attempts were made to correct the acidotic tendency, and eventually the carbon dioxide content of the plasma returned to normal. After recovery from the acute illness, the patient was followed in the hospital and in the outpatient department. The level of nonprotein nitrogen remained elevated at all times, usually at values between 50 and 60 mg. per hundred cubic centimeters.

The data were obtained during the period of persistent tendency to acidosis. As can be seen, a truly remarkable hyperosmolarity of the plasma developed, with values as high as 475 milliosmols per liter, more than 50 per cent above normal. This increase was shared by the electrolytes and the nitrogenous products. At the same time the p_H and the bicarbonate content of the plasma were reduced. This state of the plasma was maintained with some variation for over three weeks. Whatever the contribution of extrarenal factors in the causation of the hyperosmolarity of the plasma in this patient—and among them may be cited fever, insufficient intake of fluid and convulsions—without doubt, the renal anomaly was the chief factor. It is difficult to conceive how such an abnormal osmotic structure of the body fluids could have been compatible with life for an extended period and could even have proved to be reversible. Whether the mental retardation of the patient represents a congenital defect, as is likely in view of the presence of other congenital anomalies, or whether it is related to his hypocalcemia and convulsions or to the grossly abnormal electrolyte and osmotic structure of his body fluids, cannot be determined.

CASE 12.—W. Sm., a 12 year old boy, was admitted to the hospital with the history of episodes of vomiting since early childhood. The latest episode, which brought him to the hospital, had been the severest one and had lasted six days. During that time he vomited everything he took. On admission he appeared well developed, somewhat undernourished and extremely dehydrated. The body temperature was 96.5 F. Continuous intravenous administration of fluids was immediately started. He received during the first twenty-four hours 4 liters of salt-containing fluid. On the next day he appeared much improved and could sit

up, and he began to take an interest in his surroundings. After two more days of intravenous therapy, oral feedings were attempted, which were taken fairly well. However, one week later another episode of vomiting occurred. Further studies revealed a malrotation of the intestine with obstruction of the duodenum.

The data presented refer to the patient's first days in the hospital. It may be seen that on admission his plasma was hypertonic, with most of the increment above normal being derived from the retention of nonprotein nitrogen. Hypochloremia and alkalosis were present. After three days of intravenous therapy, most of which consisted of salt-containing fluids, the pattern of the plasma had changed considerably. Although the nonprotein nitrogen had dropped, the tonicity of the plasma remained at its high value, owing to a correspondingly great increase in the concentration of electrolytes. After three more days, as shown in the diagram, the osmotic and electrolyte concentrations and the p_H had returned to values within the normal range.

The increase of the osmolarity of the plasma in this patient may be explained by the complete lack of intake of fluid over a period of several days prior to admission to the hospital. A continuous expenditure of water vapor was superimposed on the losses with the vomitus of isotonic electrolyte-containing fluid. These insensible losses overtaxed the compensatory ability of the kidneys, with consequent oliguria, impairment of renal function and retention of solutes in the body fluids. The hypochloremia and alkalosis are easily explicable by the losses of hydrochloric acid with the gastric juice.

The pattern of change in the plasma during recovery suggests that the kidneys may have become adjusted to an increased osmolarity of the body fluids; despite the administration of an ample supply of fluid, the osmotic pressure remained high with return of the nonprotein nitrogen to normal and a transient increase of the concentration of electrolytes. Another, more concrete and perhaps better justified, explanation, which will be discussed further in connection with the following report of cases, is related to the type and amount of fluid therapy employed. The patient almost exclusively received salt-containing fluids for correction of his dehydration. The concentrating ability of his kidneys may well have been sufficiently impaired to permit a solute concentration of the urine only little higher than that of his blood. If such were the case, administration of isotonic solution of sodium chloride would have provided insufficient amounts of water for excretion of the excess of solutes in the body fluids. With excretion of urea the concentration of the nonprotein nitrogen in the plasma then may well have decreased at the expense of further retention of electrolytes, with consequent development of hyperelectrolytemia. If this picture corresponds to the actual events, the conclusion is justified that the treatment of the patient was unsatisfactory in that it did not supply him with

an amount of electrolyte-free fluid sufficient to provide water for maximal removal of solutes, both nitrogenous and electrolyte, by his kidneys.

In figure 5 are shown data from 2 infants with a syndrome which has been observed in 15 patients within the past two years. This syndrome, to be described in detail elsewhere, is characterized by extremely deep and rapid breathing, fever, which appears to follow the onset of the hyperpnea, impairment of the peripheral circulation, delirium and convulsions. Pathologic changes of the respiratory tract vary from mere reddening of the tracheal mucosa to moderate pulmonary involvement. In no case do the changes appear sufficient to account for the

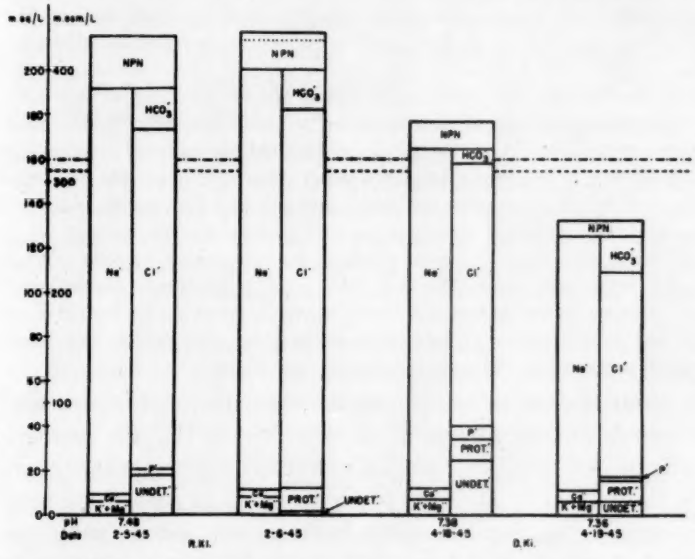

Fig. 5.—Hyperelectrolytemia and hyperosmolarity of the hyperventilation syndrome.

– . – . – . – normal electrolyte concentrations
– – – – – – – – – normal osmotic concentrations
. . . . . calculated osmolarity

extreme hyperpnea, which is the most prominent clinical manifestation of the disorder. Bacteriologic studies have failed to yield significant results. It is thought that the determining process may be a reflexogenic hyperpnea, caused by a trivial infection, which in turn is responsible for hyperpyrexia, impairment of cerebral function and vascular collapse. In addition to increased concentrations of electrolyte and nonprotein nitrogen, hypocalcemia appears to be a characteristic of the changes in the plasma and may be causally related to the tendency to convulsions. The great loss of water by way of the lungs makes this condition of particular interest in the present discussion.

Case 13 was the first of the syndrome to be studied extensively. The treatment left much to be desired in the light of later experiences and improved understanding of the condition.

CASE 13.—R. Kl., a 15 month old infant, was admitted to the hospital with a history of illness for six days. In the first four days he had vomited often and had many liquid stools. Then the diarrhea and vomiting diminished, but he began to breathe rapidly and became lethargic. Fever developed. On physical examination he appeared critically ill. He was breathing deeply and rapidly. The lips and mouth were extremely dry, and the skin was of a dry thick putty-like consistency, cool to the touch. Areas of cyanosis were present over the extremities. He was unconscious and responded only slightly to painful stimuli. The lungs were hyperresonant; the respiratory sounds were harsh. Some rales were heard over the bases of the lungs. A continuous intravenous clysis and treatment with sulfonamide compounds were begun. The clysis was continued for sixty hours. During that time a total of 3,200 cc. of fluid, 2,600 of which were saline solutions, mostly containing 5 per cent dextrose, were administered. His condition improved dramatically during the first twenty-four hours, and he was able to take milk by mouth. However, some edema developed, he became extremely irritable and the temperature reached 104 F. On the third day he suddenly suffered a collapse, with cyanosis, stiffening of the limbs and respiratory standstill. He was revived with application of artificial respiration and stimulants and was then placed in an oxygen tent. However, his condition remained poor. Cyanosis and coolness of the skin, edema and fever persisted. The next morning he had another episode of vascular collapse and respiratory standstill and died. At postmortem examination the pathologic changes in the respiratory tract were observed to be limited to acute bronchitis and several areas of pulmonary atelectasis. Congestion and edema of the brain and petechiae of the colonic mucosa were noted.

The chemical data on the plasma of this patient are represented in the first two diagrams of figure 5. It may be seen that the composition of his plasma was characterized by extremely high osmolarity, which exceeded the normal by about 50 per cent. A large part of the increase was accounted for by elevation of the levels of both sodium and chloride, which reached values of 182 and 152 milliequivalents per liter, respectively. The chloride in the spinal fluid of 161.2 milliequivalents per liter, not presented in the diagram, also indicated the extent of the hyperelectrolytemia. The concentration of bicarbonate was low, in spite of a somewhat elevated p_H, an indication of the degree of the hyperpnea and the consequent respiratory alkalosis. The plasma calcium was reduced to a value of 6 mg. per hundred cubic centimeters. The sample of plasma drawn on the following day, at the time of clinical improvement, is depicted in the second diagram. It may be seen that the concentration of the electrolytes had increased even further, with the sodium and chloride reaching values of 189 and 170 milliequivalents per liter, respectively. The nonprotein nitrogen, however, was decidedly reduced.

The most important factor in the causation of the great increase of the solute content of the body fluids of this patient undoubtedly was the

extreme degree of hyperventilation. The secondary development of fever and severe renal impairment contributed to the formation of a vicious cycle.

The course of this patient indicates that persons with extreme hyperosmolarity and renal impairment may derive little, if any, benefit from treatment with electrolyte-containing fluids alone. While the salt-containing fluid had some effect in overcoming the dehydration, no improvement of the derangement of plasma structure was apparent. The reason for this lack of efficacy of fluid therapy, at first sight surprising, probably lies in the severe impairment of renal function, which resulted in inability of the kidneys to excrete urine of high solute content. Administration of an isotonic salt solution did not provide sufficient free water for the excretion of both nitrogenous and electrolyte products. The relation of the hypocalcemia to the clinical manifestations and to the course of the disease, while beyond the scope of the present discussion, may be mentioned here.

CASE 14.—D. Ki., a 9 month old infant, had a "cold" for five days, for which he received sulfonamide drugs. The day before admission he became extremely restless, cried all the time and would not sleep at all. At that time vigorous hyperventilation began. On the morning of admission to the hospital the temperature rose to 106 F. On examination he appeared cyanotic, was breathing rapidly and forcefully and was extremely restless. Convulsive movements were present. The chest was hyperresonant. The temperature was 105 F. He was given for sixty hours continuous intravenous clysis, consisting chiefly of 5 per cent solution of dextrose in water. During the first twelve hours he received 800 cc. of fluid, and 1,900 cc. more in the next forty-eight hours. Calcium chloride in a dose of 3 Gm. daily was also administered intravenously in the first two days. His condition remained critical for the first twelve hours. Then he improved greatly; the temperature returned to normal, and he was able to take milk by mouth. After two days, hyperventilation and restlessness had subsided and no further convulsive movements were noted. However, he continued to be out of contact with the surroundings and exhibited grimacing movements and twitching of the face for about five days. All of these manifestations disappeared, and he recovered completely.

The composition of the plasma of D. Ki. on admission is depicted in the third diagram of figure 5. It may be seen that the plasma was hypertonic; the electrolyte disturbance was also reflected in the value for chloride in the spinal fluid of 143.2 milliequivalents per liter (not portrayed in the diagram). The carbon dioxide was reduced to 11 milliequivalents per liter, but the p_H was 7.38, data which are indicative of extreme hyperpnea. The effect of treatment for twenty-four hours, mostly with electrolyte-free solutions, is depicted in the fourth diagram of figure 5. It can be seen that the total concentration of solutes had dropped to 266 milliosmols per liter, 20 per cent below normal, The main constitutents contributing to the reduction were the sodium and chloride ions, which were reduced to values of 115 and 93 milli-

equivalents per liter, respectively, while the nonprotein nitrogen was still somewhat above normal limits. The great lowering of the osmolarity of the plasma following the infusion of electrolyte-free solutions at the rate employed, a procedure which does not produce such an effect in persons with normal renal function, may be taken as an indication of the profound disturbance of renal function caused by the preceding period of extreme hydropenia. A further indication of the impairment of renal function is the persistence of elevated nonprotein nitrogen values despite the administration of ample amounts of fluid. As severe as the impairment of the renal function appeared, it was reversible as is indicated by subsequent analyses, not shown in the figure but included in the table.

COMMENT

In view of the diversity of conditions presented and the multiplicity of causative factors involved, it may be of value to enumerate the factors which contribute to the development of hyperelectrolytemia and hyperosmolarity of body fluids and to point out the specific features of the metabolism of infants which predispose them to such conditions.

Water normally is expended by the body chiefly in two ways: (1) as water vapor by way of the lungs and the skin, in amounts closely related to the level of energy metabolism, and (2) via the kidneys as a carrier of solutes claiming excretion. Basically, the cause of hyperelectrolytemia may always be sought in a disparity between the supply of and the requirement for water. Complexity in causation arises from the great variety of physiologic and pathologic factors affecting the expenditure of water.

An insufficient intake of water with a normal intake of food by healthy infants has been repeatedly shown to lead to dehydration and fever.[18a] The development of fever is favored by increasing the caloric intake, particularly of protein, for two reasons: (1) because of the specific-dynamic action of protein, with increased heat production, the insensible expenditure of water is increased, and (2) because of the nitrogenous end products of protein metabolism the demand for

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Summary of Data on Plasma Composition of Fourteen Patients with Hyperelectrolytemia

Case Number; Patient	Diagnosis	Age on Admission	Weight on Admission, Gm.	p_H	Carbon Dioxide, mEq. per Liter	Chloride, mEq. per Liter	Phosphorus, Mg./100 Cc.	Total Protein, Gm./100 Cc.	Sodium, mEq. per Liter	Potassium, mEq. per Liter	Calcium, mEq. per Liter	Non-protein Nitrogen, Mg./100 Cc.	Osmolarity, Millimols per Liter	Comment
1	Gastroenteritis	9 mo.	6,700	....	7.1	145.2	7.8	...	170.6	2.7	3.4	85	...	On admission; severely dehydrated
M. Ha.				7.48	29.4	106.0	3.7	...	140.1	4.2	4.8	35	...	1 day later; improved
2	Gastroenteritis	12 mo.	8,600	....	15.1	138.8	...	...	172.3	...	4.8	27	...	On admission; dehydrated
N. Wu.					13.5	89.6	...	...	111.4	3.0	2.9	22	...	1 day later; improved
3	Gastroenteritis	1 mo.	4,200	7.30	9.3	140.8	...	...	167.5	...	4.5	71	388	On admission; dehydrated
J. Fr.					28.8	104.5	...	...	148.3	...	5.0	16	328	3 days later; improved
4	Virus diarrhea	2 mo.	2,300	....	8.2	135.2	...	...	164.9	...	4.8	90	392	Dehydrated
Dav. G.					17.9	132.8	...	...	153.1	...	4.7	35	350	1 day later; improved
5	Virus diarrhea	2 mo.	2,500	....	13.9	143.6	...	...	166.9	...	4.7	48	399	Dehydrated
Dan. G.					22.5	106.8	...	...	136.8	...	4.3	20	...	1 day later; improved
6	Erythroblastosis	3 wk.	2,300	....	16.1	147.2	...	6.1	182.3	...	5.0	78	402	On admission; severely dehydrated
W. Me.	fetalis; gastroenteritis				27.4	134.3	...	5.2	134.3	...	4.6	37	299	4 days later; improved
7	H. influenzae	8 mo.	7,800	7.21	15.9	118.0	8.2	8.0	152.5	...	3.8	106	364	On admission; dehydrated
P. Mc.	meningitis													
8	Mental retardation;	12 mo.	6,200	....	8.3	139.6	4.2	4.6	153.5	4.0	4.3	87	365	Dehydrated
M. Co.	gastroenteritis													
9	Left-sided subdural	4 mo.	6,200	....	26.8	122.8	6.3	...	162.0	4.2	5.6	72	380	
P. Ma.	hematoma													
10	Chronic gastro-	10 mo.	7,100	....	19.7	135.6	4.2	5.8	165.6	...	4.8	33	372	Dehydrated
J. He.	enteritis													
11	Gastroenteritis;	2 mo.	5,300	7.22	11.9	152.7	7.2	5.4	187.4	...	4.8	143	464	Dehydrated
L. Jo.	renal anomaly			7.08	6.3	147.8	8.8	...	167.8	...	4.0	129	416	7 days later; dehydration more severe
				7.36	32.7	119.2	5.4	5.5	171.7	6.4	3.2	97	428	Hydration improved; convulsing
12	Duodenal obstruction due to intestinal malrotation	12 yr.	35.8 Kg.	7.68	42.1	81.2	...	...	146.8	...	5.2	166	386	Dehydrated
W. Sm.				7.62	29.9	116.0	...	...	166.7	...	5.0	66	382	3 days later; hydration improved
				7.48	25.0	112.0	...	...	144.7	...	4.8	29	332	6 days later; doing well
13	Hyperventilation	15 mo.	10,100	7.48	18.8	151.6	5.2	...	181.5	...	3.2	113	430	Dehydrated
R. Kl.	syndrome				18.0	171.2	...	4.1	188.5	...	3.2	64	434	36 hours later; hydration improved
14	Hyperventilation	9 mo.	10,000	7.38	6.3	119.0	6.5	...	153.0	...	3.6	58	354	Dehydrated
D. Kl.	syndrome			7.36	15.7	93.2	2.6	...	115.1	3.2	4.4	40	266	1 day later; improved
				7.42	19.2	108.4	2.2	4.0	133.6	4.8	5.4	32	...	3 days later; doing well

renal water of excretion is greater. Addition of salt likewise may lead to the development of fever,[18] probably owing to the forced diuresis caused by an excessive supply of solutes claiming excretion. Dehydration develops more readily in young and small infants because of (1) their relatively high energy exchange and the associated high insensible water expenditure and (2) the immaturity of their renal function, with the inability to excrete urine of high solute content and consequently poor water economy.[14] In these circumstances may lie the cause of the frequent occurrence of fever (inanition fever of Holt[19]) in the newborn.[20] Fever per se, as well as externally produced elevation of the body temperature, increases greatly the insensible loss of water and by augmenting the destruction of body tissues may also increase the expenditure of water via the kidney. The increased insensible loss of water which occurs in infants with hyperventilation, either primarily central in origin or secondary to acidosis,[21] appears of particular clinical importance. A physiologic factor which may augment the requirement for water in pathologic conditions is the increased loss of water vapor caused by muscular activity and crying.[22]

All the aforementioned factors, rarely singly but often combined, play a role in pathologic conditions of childhood. Often they are superimposed on conditions of dehydration arising from loss of electrolyte containing body secretions with vomiting or diarrhea. Recognition of their importance leads to intelligent fluid management with provision of both salt-containing and salt-free repair solutions, as may be required. The estimate of the requirement must be based on clinical judgment which takes into account the history and etiology of the condition and an understanding of frequent and adequate analyses of the plasma.

The value of simultaneous determinations of the carbon dioxide, chloride and nonprotein nitrogen contents of the plasma for the char-

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20. Grulee, C. G., and Bonar, B. E.: A Peculiar Fever of Infancy, Probably Due to Depletion of the Water Reserve of the Body, Am. J. Dis. Child. **21**:220 (March) 1921. Bakwin, H., and Goss, C.: Dehydration Fever in Newborns, ibid. **24**:497 (Dec.) 1922. Bakwin, H.: Dehydration Fever in Newborns, ibid. **24**:508 (Dec.) 1922.

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acterization of its osmotic structure may be pointed out. The sum in milliequivalents of carbon dioxide and chloride, accounting for 85 per cent of the anions, is a fair indication of the total electrolyte content of the plasma, except in the presence of severe ketonemia. In the presence of an increased value for the sum of anions, caution in the employment of salt solutions is indicated. The nonprotein nitrogen in patients without renal disease is primarily an index of the water available for renal excretion, its degree of elevation providing a rough measure of the requirement for a repair solution free from salt. In the presence of elevation of both electrolytes and nonprotein nitrogen, generous administration of salt-free solution is indicated.

From the studies of the physiology of renal function of infants, it has been learned that they are incapable of excreting urine of a solute content much above that of plasma. Related to this fact may be the readiness with which edema develops in infants, since they cannot easily rid themselves of salt. Another conclusion is that salt-containing fluids alone may not provide the infantile kidney with sufficient water for excretion of accumulated solutes. This conclusion has been stressed by Aldridge [23] on the basis of studies on the effects of salt solutions in infants with diarrhea. An ample supply of salt-free solution together with an adequate amount of saline solution should answer the therapeutic needs of most patients. With respect to the type of salt-free solution it ought to be mentioned that 10 per cent dextrose solution, considered by some investigators to be harmless for infants as well as adults,[24] repeatedly has caused dehydration and hypoelectrolytemia in patients in the Children's Hospital. No such difficulty has been experienced with 5 per cent dextrose solution. A similar observation has been published by Aldridge.[23]

Differences in the response of the body to states of lack of water as compared with those arising from loss of electrolytes have been stressed by several observers.[25] In the patients with hyperelectrolytemia herein described, a thick rubbery sclerema-like consistency of the skin was prominent. It may well be, as Finkelstein and Sommerfeld

23. Aldridge, A. G. V.: The Changes in the Blood Produced by Dehydration in Infancy, Arch. Dis. Childhood **16**:81, 1941.

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hypothesized,[26] that a specific type of dehydration, namely, the hypertonic type, may manifest itself clinically by sclerematous skin.

SUMMARY

Fourteen cases of hyperelectrolytemia and hyperosmolarity in children suffering from a variety of diseases are reported. The frequency of the occurrence of hyperelectrolytemia, the factors favoring its development, particularly in infants, and the therapeutic management of the condition are discussed.

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COMPARSION OF AXILLAR AND INTRAPERITONEAL INOCULATION WITH CALMETTE-GUÉRIN VACCINE

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ACUTE infectious diseases of the gastrointestinal tract and tuberculosis have been always the two largest medical problems in Manchuria. The latter disease has apparently increased within recent years, as happens everywhere during and after wars. But since some measures against tuberculosis had been effectively undertaken, it began to diminish, at least in some places. The most remarkable results were obtained by the South Manchuria Railway Company, which employed a staff of 100,000 Japanese and 300,000 Chinese persons. They succeeded in the course of one year in reducing the number of new cases of tuberculosis to one third of the former incidence.

Along with several other preventive measures, inoculation with Calmette-Guérin vaccine was adopted, because its use had recently become popular in Japan proper and it has played an important role there in the control of tuberculosis.

The axillar method of inoculation with the vaccine, a report of which has recently been made by Takahasi [1] in Manchuria, is especially outstanding both in yielding a high percentage of positive reactions in Mantoux tests and in producing only mild local symptoms, compared with the intracutaneous and subcutaneous methods. Both these advantages, no doubt, contributed a great deal toward increased use of the vaccine. In 1945 we [2] introduced an intraperitoneal method of inoculation of young babies with Calmette-Guérin vaccine.

In this paper the result of a comparative study of these two new methods is reported.

The Calmette-Guérin vaccine which we used was contributed partly by Dr. Takahasi, Institute of Scientific Research, Hsin-King (Chang-

1. Takahasi: Cong. Proc. Jap. Tuberc. Soc., Nagoya, 1944.
2. Yamaoka, Y., and Okayasu, K.: To be published.

Chun), and partly by the Medical Department (Professor Hara) of the Manchuria Medical College.

Technic.—The child was kept standing with one side turned toward the operator (in the case of babies, lying on the table), both hands on the head, the upper arms kept horizontal. A 2 cc. syringe was used. The needle was inserted at the middle of the axillar space, upward and backward in the direction of the seventh cervical vertebra, until the tip of the needle was felt to be entirely free in the loose tissue (2 to 3 cm. deep). Occasionally some blood comes back into the syringe, in which case the needle is pulled out. There is no danger involved. Half the total dose of the vaccine was injected into each of the axillar spaces, with one injection immediately succeeding the other.

The technic followed in the intraperitoneal inoculation was the usual one. The vaccine had been previously diluted with 5 to 10 cc. Ringer's solution in 5 per cent dextrose solution to avoid possible injury to abdominal organs.

Dosage.—The dose used in this study was much larger than that ordinarily used, namely, 0.03 to 0.15 mg. in the intracutaneous inoculation and 0.02 mg. in the subcutaneous one.

RESULTS

A period of change to a positive Mantoux reaction was observed during two to thirteen weeks. The reaction ($\frac{1}{10}$ mg. to 0.1 cc.) was repeated to determine the time of appearance of tuberculous allergy, which presumably develops simultaneously with the immunity.

The table shows that in the second week 3 patients that had received axillar vaccination and 2 of the group that had received intraperitoneal vaccination had positive reactions. In the former group five sixths of all patients showed positive reactions within six weeks, while in the latter only two thirds showed positive reactions within that time.

Most subjects showed strong positive reactions in the fifth and sixth weeks in both groups, from which it was obvious that there were no remarkable differences as to final results between them. Complete allergy seemed to be delayed in infants under 3 months of age, and they were apt to react weakly. This fact is confirmed by our clinical experience.

The rate of change to a positive reaction at the end of the fifth week was 94.4 per cent in the group with axillar inoculation and 48.5 per cent in the group with intraperitoneal inoculation and in the ninth week 98.6 per cent and 96.6 per cent, respectively.

As to differences attributable to the dosage of the vaccine, there seemed to be no influence, as shown by the following figures: 0.03 mg.

was effective in 80 per cent (15 subjects), 0.06 mg. in 84 per cent (129 subjects) and 0.1 mg. in 75.3 per cent (153 subjects).

With regard to the duration of the allergic condition and simultaneous immunity, our observations were interrupted on Aug. 15, 1945. None of the subjects had died during the previous year, although certain subjects were living in a tuberculous environment. Not only in our own series, but also according to Takahasi's statistics, among more than 10,000 children and adolescents who had received inoculation with the vaccine by the axillar route, no deaths were observed during the year. Another interesting fact may be adduced. The first Dairen High School, which among seven high schools had had the highest incidence of tuberculosis and mortality (7 deaths), had no deaths

Comparison of Time Required to Effect the Change to a Positive Mantoux Reaction with Axillar and Intraperitoneal Inoculation in Infants Under Twenty-Four Months of Age

	Grade of Reaction	Period of Change to a Positive Mantoux Reaction								
		2 Weeks	3 Weeks	4 Weeks	5 Weeks	6 Weeks	7 Weeks	8 Weeks	9 Weeks	10 Weeks
Axillary inoculation										
Number of cases	+	3	3	8	19	3	5	0	1	2
	±	0	1	2	4	0	0	0	0	0
	—	6	4	3	1	0	0	0	0	0
Intraperitoneal inoculation										
Number of cases	+	2	0	5	11	12	4	2	7	4
	±	1	1	1	0	0	0	1	0	0
	—	6	6	5	2	1	0	0	0	0

from tuberculosis in the next year, when vaccination by the axillar route was made compulsory for pupils who had shown a negative reaction in a Mantoux test.

SUMMARY

The present comparative study is concerned with Calmette-Guérin vaccination of 231 subjects by the axillar, and 67 subjects by the intraperitoneal, route.

In both groups, in the second week some subjects had already begun to acquire a positive Mantoux reaction, and most of the subjects showed positive reactions in the fifth and sixth weeks. A slight difference was observed in the incidence of the change to a positive reaction within the fifth week; a greater number showed positive reactions in this week than in former weeks.

A delay in the change of the reaction among subjects inoculated by the intraperitoneal route may have been due to the fact that in this

group there were more infants under 6 months of age. In infants of this age, allergic development seems usually to be delayed and weakened. It is also considered possible that a number of more or less dystrophic babies were included.

The proportion of positive reactors in the fifth week was 94.4 per cent among the subjects inoculated by the axillar route and 48.5 per cent in those in whom the intraperitoneal route was used. There were 98.6 per cent and 96.6 per cent, respectively, in the ninth week.

As to the duration of allergy, our observations could not be concluded because of political disturbances.

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GONOCOCCIC VAGINITIS IN CHILDREN TREATED WITH A SINGLE INJECTION OF PENICILLIN IN BEESWAX AND PEANUT OIL

Report of Twenty Cases

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PENICILLIN given as a single injection in the beeswax and peanut oil mixture developed by Romansky [1] has been reported [2] to be from 80 to 100 per cent effective in the treatment of gonorrhea in adults. The present study was undertaken because to our knowledge the effectiveness of this method of administration of penicillin in a group of cases of vaginitis in children has not been reported.

MATERIAL

The patients were 20 Negro girls, ranging from 2 to 10 years of age, with uncomplicated, previously untreated gonococcic vaginitis (table). They were treated by the staff of the Chicago Municipal Social Hygiene Clinic between April 1945 and June 1946. Purulent or mucopurulent vulvovaginal exudate was present in each patient with local inflammatory signs of varying degree, often mild. At least one smear of the vaginal secretion showed typical gram-negative intracellular diplococci before treatment, which was not withheld pending report of cultures. Reactions to Kahn tests on the blood were negative in every case. One or more cultures of material from the vagina were made by a standard method [3] at intervals of two or more days after treatment. Vaginoscopic study, described in the report by Levin

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This study was under the direction of Herman N. Bundesen, M.D., Senior Surgeon (R) (inactive), United States Public Health Service; President, Chicago Board of Health.

1. Romansky, M. J.: The Current Status of Calcium Penicillin in Beeswax and Peanut Oil, Am. J. Med. **1**:395-411 (Oct.) 1946.

2. Meads, M., and Finland, M.: Penicillin in the Treatment of Gonococcal Infections: Analysis of the Results Reported in the Literature Through 1945, Am. J. Syph., Gonor. & Ven. Dis. **30**:586-609 (Nov.) 1946.

3. Carpenter, C. M., in Diagnostic Procedures and Reagents: Technics for the Laboratory Diagnosis and Control of the Comunicable Diseases, ed. 1, New York, American Public Health Association, 1941, pp. 85-112.

and Koransky,[4] was not performed. Cohn, Steer and Adler[5] have shown that asymptomatic carrier states may exist after apparent clinical cure or spontaneous remission.

Infection in 6 of our patients was traceable to the existence, within three weeks before or after diagnosis of the condition in the child, of bacteriologically proved gonorrhea in 1 or more adult members of the household. In 6 additional patients a familial source of infection was probable. The single recurrence was attributed to reinfection by a member of the family. For 2 girls, whose ages were 8 and 9 years, there was a history of rape.

TREATMENT AND RESULTS

All the girls were treated as outpatients, 2 with a single intragluteal injection of 100,000 Oxford units and 18 with a single intragluteal injec-

Bacteriologic Data on Twenty Children Treated for Gonococcic Vaginitis with Penicillin

Age, Yr.	Patient	Presence of Organism on Smear	Growth of Organism on Culture	Dose, Thousands of Units	Culture Negative for Organism, Days After Treatment	Infection in Member of Household
2	L. B.	+	+	100	3	Proved
2	J. J.	+	+	200	3	Probable
2	E. C.	+	+	200	2, 10	Proved
3	J. C.	+	+	200	2, 10	Proved
3	E. G.	+	+	200	2, 7	Proved
3	M. D.	+	..	200	2, 17	.....
3	E. K.	+	+	200	3, 233	Probable
3	L. T.	+	+	200	2	.....
3	T. J.	+	..	200	2	Probable
3	G. J.	+	+	200	3, 13	Proved
4	D. L.	+	+	200	2, 9	Proved
5*	D. A.	+	..	200	2	.....
7	R. C.	+	..	200	2, 9	.....
7	A. H.	+	+	200	2	.....
7	J. A.	+	+	200	89	Probable
8	J. B.	+	..	200	2	History of rape
8	R. H.	+	+	100	2	Probable
9	A. C.	+	+	200	2	History of rape
9	S. C.	+	+	200	44	Probable
10	D. C.	+	+	200	2, 9	.....

* The infection recurred in this patient (see text).

tion of 200,000 Oxford units of sodium penicillin, suspended in 1 cc. of a mixture of 4.5 per cent beeswax in purified peanut oil. In every patient prompt clinical remission occurred, and culture of secretion at the first post-treatment visit was negative for the organisms—for 14 this was two days after treatment; for 4, three days after treatment, and for 2, after longer periods. There was recurrence of discharge with

4. Levin, I. M., and Koransky, D. S.: Gonorrheal Vulvovaginitis in Children, Urol. & Cutan. Rev. **45**:100-107 (Feb.) 1941.

5. Cohn, A.; Steer, A., and Adler, E. L.: Further Observations on Gonococcal Vulvovaginitis, Am. J. Syph., Gonor. & Ven. Dis. **25**:329-338 (May) 1941.

appearance of the organisms on smear and culture in a 5 year old patient one hundred and twenty-two days after treatment, simultaneous with the existence of gonorrhea in her sister. She failed to return to the clinic until the one hundred and ninety-sixth day, when she was successfully treated with another injection of 200,000 units of penicillin in oil and beeswax.

COMMENT

A number of observers [6] reported that penicillin in aqueous solutions injected at three or four hour intervals in total doses of 25,000 to 350,000 units is effective in the treatment of gonococcic vaginitis in children. Sweet and Putnam,[6e] experimenting with a single injection of penicillin in aqueous solution, observed that 50,000 units was insufficient in the 3 cases tested. Sako, Tilbury and Colley,[7] using a single injection of 100,000 units in 20 cc. of isotonic solution of sodium chloride, cured 15 of their 16 patients, 13 of whom had been unsuccessfully treated with sulfonamide drugs and 10 with diethylstilbestrol. The 1 patient who did not respond was successfully retreated with divided doses of penicillin. Orally administered penicillin has been used effectively in the treatment of gonococcic vaginitis by several groups.[8]

In none of our patients were untoward reactions to treatment observed. Toxic and allergic manifestations attributable to penicillin have, however, been described.[9] Romansky [1] reported that of a series of more than 4,000 patients who received 60,000 injections of penicillin in beeswax and peanut oil, allergic reactions were encountered in approxi-

6. (*a*) Alvarez, P. J.: Penicillin in Gonococcic Vaginitis in Children, Arch. venezol. puericult. y pediat. **7**:1195-1263 (Jan.-March) 1945. (*b*) Cohn, A.; Studdiford, W. E., and Grunstein, I.: Penicillin Treatment of Sulfonamide Resistant Gonococcic Infection in Female Patients: Preliminary Report, J. A. M. A. **124**: 1124-1125 (April 15) 1944. (*c*) Greenblatt, R. B., and Street, A. R.: Penicillin for Treatment of Chemoresistant Gonorrhea in Female, ibid. **126**:161-163 (Sept. 16) 1944. (*d*) Lee, H. F., and Sussman, W.: Penicillin in the Treatment of Childhood Gonorrhea, J. Pediat. **28**:590-591 (May) 1946. (*e*) Sweet, L. K., and Putnam, L. E.: Treatment of Gonococcal Vaginitis in Children with Penicillin, M. Ann. District of Columbia **14**:148-150 (April) 1945.

7. Sako, W.; Tilbury, R., and Colley, J.: One Dose Penicillin Treatment of Chronic Gonorrheal Vaginitis in Children, J. A. M. A. **128**:508-509 (June 16) 1945.

8. György, P.; Vandegrift, H. N.; Elias, W.; Colio, L. G.; Barry, F. M., and Pilcher, J. D.: Administration of Penicillin by Mouth: Preliminary Report, J. A. M. A. **127**:639-642 (March 17) 1945. Ross, S.; Burke, F. G., and McLendon, P. A.: Penicillin by Mouth: Report of Clinical Trial, ibid. **129**:327-332 (Sept. 29) 1945. Wiederhold, A., and Mendez, A.: Ambulatory Treatment of Gonorrhea in Infants and Children with Oral Penicillin, Rev. chilena de pediat. **17**:367-380 (July) 1946; abstracted, J. A. M. A. **133**:70 (Jan. 4) 1947.

9. Kolodny, M. H., and Denhoff, E.: Reactions in Penicillin Therapy, J. A. M. A. **130**:1058-1061 (April 20) 1946. Morginson, W. J.: Toxic Reactions Accompanying Penicillin Therapy, ibid. **132**:915-919 (Dec. 14) 1946.

mately 5 per cent. In 2 of Romansky's patients sterile foreign body abscesses occurred. Severe local inflammatory reactions have been observed [10] to follow multiple injections of penicillin in beeswax and peanut oil for treatment of syphilis.

SUMMARY

Twenty girls, 2 to 10 years of age, with gonococcic vaginitis were treated with single intramuscular injections of 100,000 or 200,000 units of penicillin in beeswax and peanut oil, with prompt clinical and bacteriologic remission in each case. A single recurrence after one hundred and twenty-two days, cured by retreatment with the same method, was considered to be due to reinfection. In no cases were untoward reactions to treatment observed.

300 Longwood Avenue, Boston (Dr. Clarke).

55 West Hubbard Street, Chicago (Dr. Eisenberg).

10. Clarke, B. G.: Unpublished observations. Lederman, F. W.: A Case of Local Reaction Following the Administration of Penicillin in Beeswax and Oil, M. Rec. **159**:540-542 (Sept.) 1946.

SCARLET FEVER IMMUNIZATION

Report on Reversal of Reactions to the Dick Test Through Use of a New Type of Antigen

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AND
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INTEREST in scarlet fever immunization recently has been slight because of the present mildness of the disease and its favorable response to chemotherapy and antibiotic substances, and because the number of immunizing injections required has been large and not infrequently accompanied with general reactions. New types of antigens that require fewer injections and give only negligible reactions have reawakened interest in scarlet fever immunization.

The antigen used in this study was a refined, tannic acid–precipitated, aluminum hydroxide–resuspended scarlet fever streptococcus toxin U.S.P.[1] that contains one-tenth the alum of alum-precipitated toxoids. This preparation is more stable than the material stabilized with pectin or acacia. Three injections of 0.1 cc. each were given at monthly intervals. The doses were as follows:

	Dose	Skin Test Dose
For children	First	750
	Second	3,000
	Third	10,000
For adults	First	500
	Second	2,000
	Third	6,000

Certain groups of persons, those who are particularly exposed to streptococcic infections in their work and members of institutionalized groups, have long been considered the most suitable subjects for scarlet fever immunization.

Sixty-one student nurses who gave positive reactions to the Dick test were given the adult dose, intracutaneously in three monthly injections. There were no generalized reactions after any of the injections. Questioning elicited no recognition of fever or any report of headache,

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1. This toxin was manufactured by Lederle Laboratories, Inc., Pearl River, N. Y.

malaise or loss of time from work. Some itching and some soreness of the site when pressed, but no pain on motion of the arm, was mentioned. No sterile abscess occurred. Some persistent pigmentation (less than 4 mm. in diameter) and occasional central induration (2 mm.) were observed in many subjects after the last dose of this intracutaneous series. The Dick test, which was repeated two weeks after the completion of the series, showed reversal of reaction in 90.3 per cent of subjects. A fourth injection, a repetition of the third, brought the percentage of Dick test reversals to 100.

Thirty student nurses who gave positive reactions to the Dick test received the adult dose subcutaneously. There were no general reactions or complaints. The pigmentation that sometimes followed the intracutaneous injections was absent with the subcutaneous series. The Dick test, repeated one month after this series of subcutaneous injections, showed a reversal of reactions in 83 per cent. A fourth injection,

Reversal of Reactions to the Dick Test After Immunization with Tannic Acid-Precipitated, Aluminum Hydroxide–Resuspended Scarlet Fever Streptococcus Toxin U. S. P.

Route of Administration	Number of Patients	Reversal of Reactions to Dick Test After Three Injections, %	Reversal of Reactions to Dick Test After Four Injections, %
Intracutaneous *	61	90.3	100
Intracutaneous †	66	79	96
Subcutaneous †	66	88	100
Subcutaneous ‡	30	83	96

* This series was one of student nurses who received the injections in 1945.
† These series were of pupils in a home for feebleminded persons; alternate children received subcutaneous injections.
‡ This series was one of student nurses who received the injections in 1946.

a repetition of the third, brought reversal of reactions to the Dick test in all but 1 student. A fifth injection, a repetition of the third, secured a completely negative reaction to the Dick test in this girl.

The appropriate doses were given 132 pupils, chiefly 10 to 20 years of age, at an institution for mentally defective persons who showed positive reactions to the Dick test. Pupils 13 years of age and younger received the children's dose; those 14 years of age and over, the adult dose. Alternate subjects were given the series of three monthly injections subcutaneously; the others received intracutaneous injections, as described previously. There were no generalized reactions. Transient soreness and itching occurred at the site of the injection in some cases. A reversal in the reaction to the Dick test was obtained in 79 per cent of the subjects receiving the intracutaneous series and in 88 per cent of the subjects receiving the subcutaneous series. A fourth injection, a repetition of the third, secured a reversal in the reaction to the Dick test in the few persons whose reactions were persistently positive, except

in the case of 2 older girls, 1 a pituitary dwarf, in the series who received intracutaneous injections.

The subcutaneous method yielded the same high percentage of reversal of reactions to the Dick test; it also caused no general reaction, and the skin was free of the slight pigmentation and the tiny area of induration which often occurred at the site of the third intracutaneous injection. Moreover, administration by the subcutaneous route was even easier and was less painful to the patient.

SUMMARY

A high percentage (80 to 90) of reversal of reactions to the Dick test was obtained in over 200 persons after the intracutaneous or subcutaneous injection of three monthly doses of 0.1 cc. each of a new scarlet fever streptococcus toxin. This percentage reached practically 100 when one repetition of the third dose was given after a persistently positive reaction to the test. Scarlet fever has not occurred in any of the immunized subjects since this study began. No generalized reaction occurred. The subcutaneous route of administration is recommended.

University Hospital.

AID TO INTERPRETATION OF CHANGES IN THE CEREBROSPINAL FLUID IN PEDIATRIC CASES

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AND
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OCCASIONAL errors in the interpretation of changes in the cerebrospinal fluid prompted us to devise a simple chart which would serve as a helpful guide in the differential diagnosis of neurologic conditions. The chart presented here is the result. There is nothing original about it except its arrangement. It is to be used only as a guide, and we wish to emphasize that it is not intended to supplant a careful consideration of the history and physical findings.

Normal values are represented by a horizontal line; values higher than normal, by diagonal lines above the horizontal, and values below normal, by a descending diagonal line. Pressure, being subject to individual interpretation and varying with the response of the child to the procedure, is placed at the right of the chart where its significance can be more carefully evaluated.

The chart has been utilized for several months and found useful. Several revisions have been made during this period, and further revisions will, no doubt, be made. Recheck of several difficult and obscure neurologic problems has demonstrated its value in reducing diagnostic confusion.

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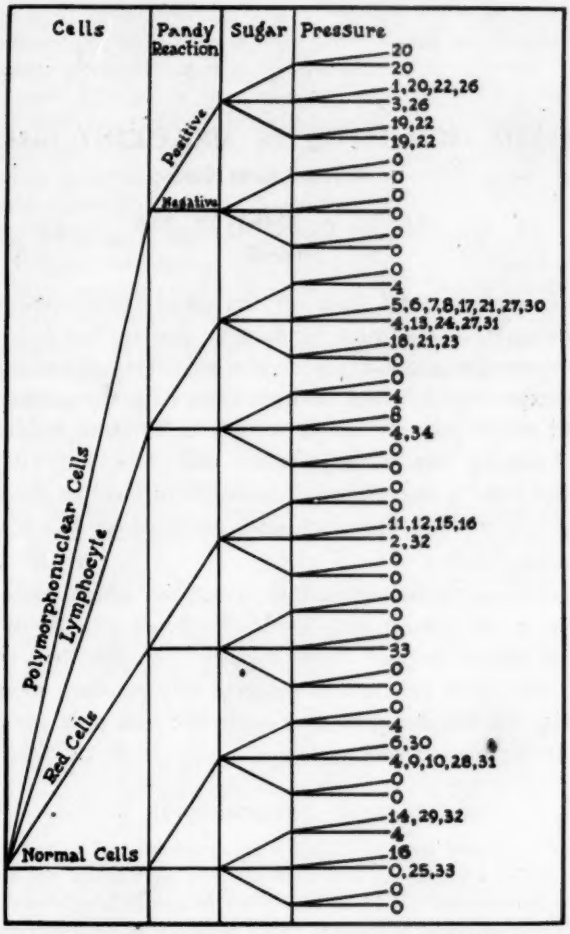
From Milwaukee Children's Hospital.



*Scheme for evaluation of changes in the cerebrospinal fluid. 0 indicates the absence of disease; *1*, cerebral abscess; *2*, bloody fluid obtained on tap, and *3*, cerebral softening. *4* indicates epidemic type A (lethargica) encephalitis; *5*, epidemic type B (St. Louis); *6*, lead encephalitis; *7*, measles encephalitis, and *8*, mumps encephalitis. *9* indicates Froin's syndrome; *10*, the Guillain-Barré syndrome; *11*, subdural hematoma; *12*, subarachnoid hemorrhage, and *13*, juvenile dementia paralytica.

14 indicates thrombosis of the lateral sinus; *15*, nonseptic sinus thrombosis, and *16*, meningismus. *17* indicates lymphocytic choriomeningitis; *18*, meningococcic (early) meningitis; *19*, purulent meningitis; *20*, serous meningitis; *21*, acute syphilitic meningitis; *22*, tuberculous (early) meningitis, and *23*, tuberculous (late) meningitis.

24 indicates active multiple sclerosis; *25*, inactive multiple sclerosis; *26*, the early stage of poliomyelitis; *27*, a later stage of poliomyelitis; *28*, polyneuritis; *29*, fluid obtained on tap after convulsion; *30*, brain tumor; *31*, intraspinal tumor; *32*, uremia; *33*, xanthochromia of the newborn, and *34*, response to sulfonamide therapy.

Normal values are represented by a horizontal line; values higher than normal, by diagonal lines above the horizontal, and values below normal, by a descending diagonal line.

SERUM IRON LEVELS IN ADOLESCENT GIRLS

A Study of Three Cases

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USABLE experimental data on the iron requirement of children are meager. This want of data is due to the lack of a good method of determination. Most of the available information is based on balance experiments which furnish valid data for adults, but which fail to yield much information in regard to children because there is no way of knowing how large retention should be. In 1942 Johnston and Roberts [1] tried using a normal hemoglobin level as the criterion of adequacy. This method furnishes some information, but it has definite limitations.

In the search for a better method, it seemed worth while to investigate the use of the serum iron level. Evidence existed in the literature [2] that it might respond more rapidly than the hemoglobin level. Adolescent girls were selected as subjects because they should respond rapidly, owing to the fact that they need iron not only for growth but also for covering menstrual losses.

PRESENT INVESTIGATION

The values for serum iron of 4 girls were determined. The results for 1 subject were discarded because she had a serum iron level below the normal range. The other 3 subjects were 13, 14, and 14 years of age and weighed 127, 88½ and 92½ pounds (57.6, 40.2 and 41.9 Kg.). They were placed on a diet providing 4 to 5 mg. of iron for nine weeks. After that, the diet had to be made less rigid because the subjects were volunteers and could not be asked to continue longer on a monotonous dietary regimen. The intake was raised to approximately 9 mg. for six weeks, and then to about 11 mg. for six weeks more. These intakes were higher than they first appear because all 3 subjects were only about 5 feet (152 cm.) tall.

In order to reduce the number of analyses of food, the menus were planned on a two week basis. The foods served in the second week were a duplicate of those served in the first week. An exception to this rule occurred when the same

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This study was supported in part by a grant from the Nutrition Foundation, Inc.

1. Johnston, F. A., and Roberts, L. J.: The Iron Requirement of Children of the Early School Age, J. Nutrition **23**:181 (Feb.) 1942.

2. Leverton, R. M.: Iron Metabolism in Human Subjects on Daily Intakes of Less than 5 Milligrams, J. Nutrition **21**:617 (June) 1941.

menu was repeated three times, for weeks 7, 8 and 9. One-fifth aliquots of the food were weighed out three times a week and combined into a weekly composite. These composites were blended in a Waring blender and digested with heat and hydrochloric acid. Samples of the digest were wet ashed, and iron was determined by the thiocyanate method of Stugart.[3] The milk, bread and water were analyzed separately. All ten digests for subject B were analyzed, but only two each for subjects A and C, because their intakes were similar to those of subject B. The results are recorded in table 1.

Samples of blood were taken at frequent intervals. Ten and one-half cubic centimeters of blood was drawn after the subject had been sitting quietly for forty-five minutes to eliminate the effect of exercise. Determinations were made of the hemoglobin, cell volume, cell count and serum iron. The hemoglobin contents were determined by the method of Evelyn,[4] and the red blood cell volumes, by the turbidity method of Shohl.[5] Both methods were adapted to the Coleman spectrophotometer. The cell counts were made in duplicate on each of two samples of blood. The first determinations were discarded because the subjects were excited. The results are reported in table 2.

TABLE 1.—*Average Iron Intake per Day for One Week Periods*

Week	Daily Iron Intake, Mg.		
	Subject A	Subject B	Subject C
1	....	3.76	....
3	....	4.92	....
5	5.26	5.34	4.32
7	....	4.16	....
10	....	8.90	....
12	....	9.08	....
14	8.75	9.97	8.09
16	....	11.05	....
18	....	11.08	....
20	....	11.09	....

The red cell volumes, of 41.5, 42.1 and 41.8 per cent; the red cell counts, of 4,130,000, 4,220,000 and 4,130,000 per cubic millimeter, and the hemoglobin levels, of 13.3, 13.3 and 13.3 Gm. per hundred cubic centimeters, were similar for all 3 subjects. That these values were average for this age is evident from the reports in the literature. Osgood and Baker[6] found a mean of 12.92 Gm. of hemoglobin and 5,130,000 red cells for 10 girls 13 years of age. Leichsenring, Donelson and Wall[7] reported a mean of 12.05 Gm. of hemoglobin and 4,200,000 red

3. Stugart, R.: Determination of Iron in Milk and Other Biological Materials, Indust. & Engin. Chem. (Anal. Ed.) **3**:390 (Oct. 15) 1931.

4. Evelyn, K. A.: A Stabilized Photoelectric Colorimeter with Light Filters, J. Biol. Chem. **115**:63 (Aug.) 1936.

5. Shohl, A. T.: The Measurement of Cell Volume of Blood by the Cell Opacity Method, J. Lab. & Clin. Med. **25**:1325 (Sept.) 1940.

6. Osgood, E. E., and Baker, R. L.: Erythrocyte, Hemoglobin, Cell Volume and Saturation Index Standards for Normal Children of School Age, Am. J. Dis. Child. **50**:343 (Aug.) 1935.

7. Leichsenring, J. M.; Donelson, E. G., and Wall, L. M.: Studies of Blood of High School Girls, Am. J. Dis. Child. **62**:262 (Aug.) 1941.

cells for 43 healthy girls 14 years of age. Wiehl[8] observed a mean of 13.7 Gm. of hemoglobin (as interpreted from a chart) for a group of 17 to 34 girls 13 years of age and for the same number of girls 14 years of age from high income families. Of the latter group a number had been eliminated because of physiologic conditions that might affect adversely the hemoglobin level. All the values reported by the

TABLE 2.—*Determinations Made on the Blood of Three Adolescent Girls*

Date	Approximate Iron Intake, Mg./Day	Volume of Red Cells, %			Hemoglobin, Gm./100 Cc.		
		Subject A	Subject B	Subject C	Subject A	Subject B	Subject C
January 12	Ad lib.	41.5	47.0	44.5	12.6	14.1	13.8
January 19	4-5						
January 24	....	44.8	44.0	43.5	13.9	13.5	13.4
March 13	....	42.5	43.5	43.5	13.4	13.4	13.3
March 20	....	41.5	42.0	41.3	13.6	13.3	13.5
March 23	9-11						
April 5	....	40.4	38.0	41.3	13.4	12.5	13.0
April 19	....	43.0	43.0	42.0	13.5	13.2	13.2
May 4	....	42.5	43.3	43.3	13.2	13.5	13.2
May 18	....	42.5	42.5	....	13.2	13.2	....
June 1	....	41.5	41.5	41.5	13.6	13.2	13.2
June 8	....	39.0	41.3	41.0	12.9	13.1	13.2
June 14	....	37.5	37.5	36.0	12.9	12.9	12.8
Mean	....	41.5	42.1	41.8	13.3	13.3	13.3
		Red Cell Count, Millions/Cu. Mm.			Serum Iron, Micrograms/100 Cc.		
January 12	Ad lib.	4.16	4.50	4.43	69	81	57
January 19	4-5						
January 24	....	4.36	4.47	4.36	70	60	51
March 13	....	4.08	4.14	4.34	80	57	40
March 20	....	4.36	3.81	4.49	80	60	40
March 23	9-11						
April 5	....	4.13	4.21	4.22	89	74	48
April 19	....	4.33	4.53	3.35	85	49	45
May 4	....	4.16	4.29	4.29	93	77	67
May 18	....	4.24	4.67	....	41	54	..
June 1	....	4.58	4.25	3.83	40	45	40
June 8	....	3.70	3.57	4.31	74	57	37
June 14	....	3.36	3.99	3.72	70	63	38
Mean	....	4.13	4.22	4.13	72	62	46

aforementioned authors were obtained by means of single determinations and probably were the results of first determinations in many cases. It is the experience of my associates and me that a few children become so frightened at the time of a first test that their values are high. One of these 3 subjects reacted in that way. Her hemoglobin in the first determination was 14.9 Gm., and in the second, 14.1 Gm.; then

8. Wiehl, D. G.: Selecting Cases of Anemia Among Adolescents, Am. J. Pub. Health **31**:1073 (Oct.) 1941.

the values leveled out at 12.9 to 13.5 Gm. The same thing was true of her blood cell count. For this reason, it is our practice to discard the data from first determinations.

The serum iron was determined by the method of Powell,[9] as modified by McCance, Edgecombe and Widdowson[10] to require only 2 cc. of serum. The serum was treated with hydrochloric acid to separate the iron from the protein; the protein was precipitated with trichloroacetic acid; the filtrate was heated with a drop of nitric acid, and iron was determined by the thiocyanate method. Recoveries of 92, 98 and 119 micrograms per hundred cubic centimeters, respectively, were considered satisfactory. Three samples of pooled human serum gave values of 105, 115 and 119 micrograms, respectively, per hundred cubic centimeters which are near the average for normal subjects. A comparison of methods of determining serum iron which is in progress in our laboratory shows that this method gives values 10 to 20 per cent below those demonstrated by the method of Kitzes, Elvehjem and Schuette.[11]

The results of the serum iron determinations are reported in table 2; mean values for eleven determinations on the 3 subjects were 72, 62 and 46 micrograms, respectively, per hundred cubic centimeters. Most of the values for subject C were below 50 micrograms, which is usually accepted as the lower limit of the normal range. In a study of the serum iron levels of 23 girls 14 and 15 years of age, Vahlquist[12] reported a mean of 122 micrograms. Even if the values for the 3 subjects of the study are raised 20 per cent to give the highest values that would have been obtained had the method of Kitzes and associates[11] been used, they are still below the mean value reported by Vahlquist.[12]

The possibility that the values for serum iron for these subjects might have been low because the samples of blood were drawn in the late afternoon was suggested by the work of Hemmeler[13] and Vahlquist,[14] both of whom reported a fall in the serum iron level during the day. To check this possibility, a set of determinations was made on fasting blood at 8:00 a. m. The resulting values were no higher than ones obtained on blood taken at 5:30 p. m. and were, therefore, included in table 2 for March 20. These data are in agreement with

9. Powell, J. F.: Serum-Iron in Health and Disease, Quart. J. Med. **13**:19 (Jan.) 1944.

10. McCance, R. A.; Edgecombe, C. N., and Widdowson, E. M.: Phytic Acid and Iron Absorption, Lancet **2**:126 (July 31) 1943.

11. Kitzes, G.; Elvehjem, C. A., and Schuette, H. A.: The Determination of Blood Plasma Iron, J. Biol. Chem. **155**:653 (Oct.) 1944.

12. Vahlquist, B.: Das Serumeisen, Acta pædiat., 1941, supp. 5.

13. Hemmeler, G.: Nouvelles recherches sur le métabolisme du fer; les oscillations du fer sérique dans la journée, Helvet. med. acta **11**:201, 1944.

14. Vahlquist, B., in discussion on Waldenström, J.: Om järnomsättningen vid perniciös anämi, Nord. med. **8**:2287, 1940.

those of Moore and associates [15] who found no evidence of a downward drift during the day.

The levels of serum iron for subjects A and B showed no tendency to fall during the nine week period on the low iron diet or to rise on the higher intakes. The level of subject C fell somewhat on the low iron diet. This fall was within the normal day to day fluctuation. Nevertheless, it may have had some significance because it remained low. This subject might have responded more quickly to the low iron diet than the other 2 because her menstrual losses, as judged from the duration of the periods and the number of pads used, were much greater. Her level appeared to be rising on the higher intake, then she contracted an infection of the upper respiratory tract on May 16 and her level fell. Since the serum iron levels of these subjects who already had low levels did not fall significantly over a nine week period on a low iron intake, or rise over a period of twelve weeks on a fair or good iron intake, it must be concluded that the serum iron level does not respond to dietary intake quickly enough for use as the criterion of adequacy in carefully controlled metabolic studies which must be of short duration. This study does not prove that it will not respond over a longer period. It, also, does not prove that the serum iron level is no better a criterion than the hemoglobin level.

Why the levels of the 3 subjects were different is not known with any degree of certainty. The low levels for subject C are easily explained by her large menstrual losses. Subject A, whose level was the highest of the 3 girls, probably had been obtaining a higher iron diet than the other 2 because her total food consumption had been greater previous to the experimental period. The fourth girl who volunteered to serve as a subject, but who was not accepted because her serum iron level was only 20 micrograms per hundred cubic centimeters, had been eating almost no meat for years.

Several reports have been made in the literature of rather wide variations in serum iron in the same subject over a period of time. Typical of them is one by Moore and associates,[15] who determined the serum iron of 16 women at frequent intervals for six months and reported an average difference of 41 micrograms between minimum and maximum values. In the present study the average difference was 35 micrograms. However, most of the values for a given subject lay within a range of 20 micrograms. In the case of subject A the two determinations made on May 18 and June 1 were outside this range. During that period the subject had a cold. She was, however, susceptible to colds and had several during the course of the study; possibly

15. Moore, C. V.; Minnich, V., and Welch, J.: Studies in Iron Transportation and Metabolism: III. The Normal Fluctuations of Serum and "Easily Split-off" Blood Iron in Individual Subjects, J. Clin. Investigation **18**:543 (Sept.) 1939.

this cold was severer than the others. A variation of 20 micrograms is not wide when the experimental error, which is at least 10 micrograms, is taken into account. If the variation observed in this study is typical, normal fluctuations are not large enough to obscure changes in serum iron levels from the average range of 100 to 120 micrograms to abnormal levels of 50 or 60 micrograms or below.

The fact that the hemoglobin levels of all the subjects were near average values for girls but the serum iron levels were low and differed among the subjects suggests the possibility that the serum iron level may be a more sensitive indicator of iron stores than the hemoglobin level. This idea is further substantiated by values for the fourth girl, whose serum iron was only 20 micrograms per hundred cubic centimeters but whose hemoglobin measured 13.1 Gm. per hundred cubic centimeters and whose cell count was 4,500,000 per cubic millimeter.

SUMMARY

The hemoglobin levels, red cell volumes and red cell counts of 3 adolescent girls taken eleven times over a period of five months were in the average range for girls and were similar for all 3 subjects. The mean serum iron levels of 72, 62 and 46 micrograms, respectively, per hundred cubic centimeters were low, differing among the 3 subjects. This variation suggests the possibility that serum iron may respond more rapidly to changes in iron stores than does the hemoglobin content, the cell count or the cell volume.

If serum iron does respond more rapidly than hemoglobin, the response is not rapid enough to use as the criterion for studies of the iron requirement which are of a few weeks' duration. The serum iron of the 3 subjects did not decrease on an intake of 4 to 5 mg. of iron for nine weeks, or rise on an intake of 9 to 11 mg. for eleven weeks.

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Case Reports

ACUTE INFECTIOUS LYMPHOCYTOSIS

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THE RECOGNITION of acute infectious lymphocytosis as an entity separate from infectious mononucleosis dates from Smith's [1] report in 1941. Since that time the number of reported cases of this condition has increased, until at this writing 38 have been published. The series of Reyersbach and Lenert [2] undoubtedly must be of this nature, and Smith, in his recognition of the entity, made reference to the report of these investigators.

Smith designated infectious lymphocytosis as being acute or chronic and established definite criteria for the diagnosis as differentiated from lymphatic leukemia and infectious mononucleosis.

The disease is termed infectious because it has occurred in small epidemics.[3] Recently, Lorenz, Hardy and Alt [4] reported the disease in 2 brothers.

Most reports have been of young children under the age of 6 years, although Duncan [5] and Yuskis [6] recorded cases of the condition in young adults. The symptoms are remarkably mild, and in not a few of the cases [3c] the condition has been accidentally discovered in examination for other diseases.

In children it is most important to differentiate the disease from lymphatic leukemia and, less pointedly, from infectious mononucleosis.

In children the differentiation of the condition from leukemia lies in the fact that although the lymphocytes are increased in number they are small and of normal appearance and no immature forms appear in the peripheral blood. The number of platelets is not decreased and there is no accompanying anemia.

Differentiation from infectious mononucleosis presents a more difficult problem. In this disease the patient is more acutely ill; the lymph

1. Smith, C. H.: Infectious Lymphocytosis, Am. J. Dis. Child. **62**:231-261 (Aug.) 1941.

2. Reyersbach, G., and Lenert, T. F.: Infectious Mononucleosis Without Clinical Signs or Symptoms, Am. J. Dis. Child. **61**:234-237 (Feb.) 1941.

3. (*a*) Reyersbach and Lenert.[2] (*b*) Finucane, D. L., and Philips, R. S.: Infectious Lymphocytosis, Am. J. Dis. Child. **68**:301-307 (Nov.) 1944. (*c*) Smith, C. H.: Acute Infectious Lymphocytosis, J. A. M. A. **125**:342-350 (June 3) 1944.

4. Lorenz, M.; Hardy, M., and Alt, H. L.: Infectious Lymphocytosis, J. A. M. A. **131**:882-883 (July 13) 1946.

5. Duncan, P. A.: Acute Infectious Lymphocytosis in Young Adults, New England J. Med. **233**:177-179 (Aug. 9) 1945.

6. Yuskis, A. S.: Infectious Lymphocytosis, J. A. M. A. **132**:638-639 (Nov. 16) 1946.

nodes and the spleen may be enlarged, and the predominant cells are large atypical lymphocytes. The Paul-Bunnell test gives a positive reaction in a rising titer as the disease progresses.

Infectious lymphocytosis in childhood has a variable onset. Often no symptoms exist. There may be malaise, sore throat and vomiting. Rashes have been reported, and the symptom of drowsiness has led some investigators [7] to perform a lumbar puncture. These punctures have shown an increase in cells of the lymphoid series in the spinal fluid. In none of the cases recorded has the reaction to the Paul-Bunnell test been positive to a significant degree,[4] and in none has there been any enlargement of the spleen and the lymph nodes.

Studies of the bone marrow in the acute phase of the disease by Smith [3c] showed an increase in the cells of the lymphoid series and, in

TABLE 1.—*Blood Counts of a Child with Acute Infectious Lymphocytosis*

Date	Hemoglobin, %	White Cell Count	Polymorphonuclear Leukocytes: Young Forms	Polymorphonuclear Leukocytes: Old Forms	Monocytes	Eosinophils	Lymphocytes	Basophils	Platelets
11/ 9/46	75	39,350	3	25	2	1	69	0	Clumps
11/13/46	88	24,400	8	12	3	8	69	0	Clumps
11/18/46	80	14,300	8	18	1	2	68	3	Clumps
11/23/46	78	16,800	17	11	7	1	61	3	Clumps
11/18/46	Reaction for heterophil antibodies negative; sedimentation rate, 14 mm./hr. (Westergren)								

TABLE 2.—*Study of Bone Marrow in Acute Infectious Lymphocytosis* *

Myeloblasts	0.8	Polymorphonuclears, mature neutrophilic	6.2	Prolymphocytes	0.8
Promyelocytes	4.8	Eosinophils (all)	3.6	Monocytes	1.8
Myelocytes, neutrophilic	9.4	Plasma cells	0.2	Erythroblasts	4.6
Metamyelocytes, neutrophilic	13.8	Disintegrated cells	5.4	Normoblasts	8.6
Polymorphonuclears, young neutrophilic	17.0	Lymphocytes	22.2	Megakaryocytes	Normal
				Cell count	90,000

* Values expressed per hundred cells.

the stage of recovery, a normal marrow. Biopsy of the lymph nodes during the acute phase [3c] showed proliferation of the reticuloendothelium of the sinuses, which may become blocked with masses of these cells. Some germinal centers showed hyaline degeneration.

REPORT OF A CASE

I. F., aged 4 years, was seen because of a history of vomiting for four days and drowsiness for one day. The past illnesses and the family history were noncontributory. There was no history of exposure to pertussis.

Physical examination showed a listless, undersized child. Her temperature was 100.2 F. by rectum; the pulse rate was 100 and the respiratory rate 16 per minute.

7. Thelander, A. E., and Shaw, E. B.: Infectious Mononucleosis with Special Reference to Cerebral Complications, Am. J. Dis. Child. **61**:1131-1145 (June) 1941. Beloff, J. S., and Gang, K. M.: Acute Poliomyelitis with Acute Infectious Lymphocytosis, J. Pediat. **26**:586-592 (June) 1945.

The tonsils were moderately enlarged, and the pharynx was slightly injected. The spleen and lymph nodes were not palpable, and the remainder of the examination showed nothing abnormal. It was striking that although the child was obviously ill nothing could be elicited on physical examination. The urine gave a positive reaction for ketones and was normal in all other respects. The roentgenogram of the chest showed nothing abnormal. The white cell count was 39,350, with 69 per cent small lymphocytes, 28 per cent polymorphonuclear leukocytes, 2 per cent monocytes and 1 per cent eosinophils, and platelets were present in large numbers and in clumps. No abnormal cells were seen, and the hemoglobin content was 11.5 Gm. per hundred cubic centimeters.

The data on studies of the blood counts made during her stay in the hospital are recorded in table 1, and the results of a study of the bone marrow on her ninth day in the hospital are presented in table 2.

After entering the hospital, she stopped vomiting, and her appetite rapidly returned. On November 22 pain and swelling developed at the site of the marrow puncture over the left tibia.

COMMENT

The condition described satisfies the criteria for a diagnosis of infectious lymphocytosis. A striking feature of her blood picture was the rise in eosinophils on November 13. This elevation was also noted in the cases reported by Smith [1] and Finucane and Philips.[3b]

This child was persistently drowsy; this symptom might have led to a lumbar puncture had she had any other neurologic signs and had she not improved so rapidly in the hospital. The importance of differentiation from leukemia is obvious; infectious lymphocytosis carries no mortality.

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DIPLOCOCCUS MUCOSUS MENINGITIS SUCCESSFULLY TREATED WITH SULFADIAZINE AND PENICILLIN

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PYOGENIC meningitis in infancy and early childhood generally falls into one of the following groups [1]: (1) meningococcic, (2) influenzal, (3) pneumococcic, (4) staphylococcic, (5) coliform or (6) streptococcic. However, occasionally cases are encountered in which an organism of low pathogenicity, such as the Micrococcus tetragenus [2] or the Diplococcus mucosus,[3] is the etiologic agent. Because of its morphologic and staining characteristics, the D. mucosus may readily be confused with the meningococcus. It is the purpose of this paper to present a case in which this organism, when observed on direct smears from the spinal fluid as a gram-negative intracellular and extracellular diplococcus, was erroneously interpreted as a meningococcus. The distinguishing bacteriologic characteristics of the D. mucosus are discussed. The chemotherapeutic measures and antibiotic substances employed in this case are also discussed.

REPORT OF A CASE

During the height of a minor outbreak of meningococcic infections, on Feb. 2, 1946, a 3 month old white girl was admitted to the pediatric service of the Nashville General Hospital, with a complaint of fever and hyperirritability. The parents dated the present illness from six days prior to hospitalization, at which time the infant became irritable and had a low grade fever, which persisted for four days without obvious cause. On the fifth day the elevation in temperature became more pronounced, and the family physician was summoned. He diagnosed the condition as

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1. Levinson, A., in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1944, vol. 4, chap. 8, p. 26.

2. Criscitiello, M., Jr.: Meningitis Due to the Micrococcus Tetragenus, New England J. Med. **221**:383-385 (Sept. 7) 1939.

3. (*a*) Topley, W. W. C., and Wilson, G. S.: Principles of Bacteriology and Immunity, ed. 3, revised by G. S. Wilson and A. A. Miles, Baltimore, Williams & Wilkins Company, 1946, p. 553. (*b*) Cowan, S. T.: Unusual Infections Following Cerebral Operations, Lancet **2**:1052-1054 (Nov. 5) 1938. (*c*) McFarlan, A. M.: Diplococcus Mucosus von Lingelsheim: A Description of a Strain with Comment on the Systematic Position of the Organism, J. Path. & Bact. **53**:446-450 (Nov.) 1941. (*d*) Bray, P. T., and Cruickshank, J. C.: Meningitis Due to the Diplococcus Mucosus, Brit. M. J. **1**:601-602 (May 15) 1943.

a "cold" and prescribed acetylsalicylic acid, 0.15 Gm., every four hours. She was hospitalized the following day when a bulging anterior fontanel developed. There was no history of vomiting, convulsions or other neurologic disturbance. Birth and the developmental history were normal, and there was no family history of tuberculosis or syphilis.

Physical examination revealed a well developed and well nourished white girl, weighing 11 pounds (4,990 Gm.). She appeared acutely but not critically ill and was irritable, but in no immediate distress. The temperature on admission was 105.2 F. The skin was hot and dry, with somewhat diminished turgor, but was free of rash or petechiae. Examination of the head revealed pronounced bulging of the anterior fontanel. There was no evidence of inflammation of the ears, nose or throat. Examination of the heart, lungs and abdomen showed nothing abnormal. Neurologic examination revealed the neck to be remarkably supple, with a negative Brudzinski sign. There was a questionable Kernig sign. The deep tendon reflexes were equal and somewhat hyperactive. No other pathologic reflexes were noted.

Laboratory Data.—Studies of the blood showed that the hemoglobin content was 12 Gm., the red cell count 4,260,000 and the white cell count 8,550, with 75 per cent polymorphonuclear cells; culture of the blood yielded a gram-variable coccus. The urine gave a 1 plus reaction for albumin, with 10 red blood cells per high power field; culture of the urine yielded no growth. Wassermann and Kline reactions of the blood were negative.

Lumbar puncture performed on her admission to the hospital yielded 10 cc. of slightly cloudy spinal fluid under moderate increase in pressure. There were 200 cells per cubic millimeter, of which 86 per cent were polymorphonuclear leukocytes and 14 per cent were mononuclear cells. Quantitative determinations of protein and sugar showed 185 and 35 mg. per hundred cubic centimeters, respectively. A Gram stain of the uncentrifuged fluid, performed by the house officer on the patient's admission, revealed large numbers of gram-variable cocci, occurring in diploid and tetrad forms. These organisms were recovered culturally on the first day in the hospital but not thereafter. Blood cultures also yielded the organisms on the first and third days in the hospital but not after the third day, February 4.

Course in Hospital.—After making a tentative diagnosis of meningococcic meningitis, the house officer administered 10,000 U.S.P. units of antimeningococcic serum intramuscularly, 100 cc. of plasma intravenously and a hypodermoclysis of 100 cc. of sixth-molar lactate solution, which contained 1 Gm. of sulfadiazine sodium. Eight hours later maintenance sulfadiazine therapy, with a dose of 0.375 Gm. every four hours, was instituted. The level of sulfadiazine in the blood was 9.1 mg. per hundred cubic centimeters on the following day. The dose of sulfadiazine therefore was increased to 0.5 Gm. every four hours. On February 5 the blood level of the drug had risen to 19.8 mg. per hundred cubic centimeters.

The spinal fluid, examination of which on February 4 had shown 240 white blood cells, proved on culture to be free of viable organisms.

Although the patient appeared somewhat improved generally, it was thought unwise to continue with sulfadiazine therapy alone when on February 5 her temperature rose to 103 F. Penicillin therapy was instituted; 15,000 U.S.P. units was administered intramuscularly every three hours. She was also given intrathecally 10,000 units of penicillin dissolved in 6 cc. of spinal fluid. Within a few hours her temperature became normal and remained so. The intrathecal administration of penicillin was repeated for the next three days in amounts of 5,000, 10,000 and 10,000 units The spinal fluid on February 7 revealed only 40 cells per cubic millimeter, which were predominantly mononuclear. Quantitative determination of

protein showed 97 mg. per hundred cubic centimeters, and culture of the spinal fluid yielded no organisms. No quantitative determination of sugar was performed.

Severe serum sickness, characterized by fever, vomiting and an erythematous macular rash, which showed relatively uniform distribution over the trunk and extremities, developed on February 7. The patient was given 100 mg. of diphenhydramine hydrochloride ("benadryl hydrochloride"[4]) as the initial dose, and in four hours the rash had almost completely disappeared. She was maintained on 50 mg. of the drug every four hours. All evidence of the serum sickness had cleared in eight hours.

The diphenhydramine hydrochloride was discontinued after twenty-four doses, and in eighteen hours the serum rash reappeared. Therapy was reinstituted, and the rash disappeared after one dose of 75 mg. and was absent during the succeeding two days of therapy with 50 mg. every four hours. The rash reappeared on February 15, twelve hours after therapy was discontinued, and consisted of a few scattered lesions, which disappeared slowly during the next twenty-four hours without treatment.

The patient continued to improve rapidly, all signs of meningitis having disappeared by February 7. On February 11 her temperature again rose to 101 F. This elevation was thought to be a reaction to the sulfadiazine. The fever promptly disappeared after administration of this drug was discontinued.

Penicillin was discontinued on February 15. The infant remained in the hospital for forty-eight hours longer, during which time her temperature remained normal.

Examination just prior to discharge revealed no abnormality, the patient being alert, playful and apparently in excellent condition. She since has grown and developed normally, with no recurrence of the infection.

BACTERIOLOGIC STUDIES

Because of the relatively rare occurrence of D. mucosus as a pathogenic organism, the bacteriologic data will be given in some detail.

Morphologic and Staining Characteristics.—Smears of the spinal fluid revealed a gram-variable coccus arranged in pairs and tetrads, rarely in clumps. The organisms, which showed decided variation in size, were observed both intracellularly and extracellularly.

Gram stains of organisms taken from many identical colonies showed almost 5 per cent gram-variable forms, the remainder being gram-negative. The capsule was demonstrated by the method of Welch to be a large, clearly defined structure.

Cultural Characteristics.—The spinal fluid was cultured on both blood and chocolate agar at 37.5 C. for twenty-four hours. There were many grayish, semitranslucent, nonhemolytic colonies, which varied from 1 to 2 mm. in diameter. The typical colony was round and convex, with regular, entire edges and a shiny, smooth appearance. The consistency was somewhat viscous and mucoid; however, the colonies were easily emulsified. The growth was luxuriant, with a tendency to become confluent. After four days, the colonies usually measured 2 to 5 mm. in diameter and were often umbonate with undulant margins, which showed fine radial striations.

4. "Benadryl hydrochloride" is the trade name of Parke, Davis & Company for beta-dimethylaminoethyl benzohydryl ether hydrochloride. This drug was furnished through the courtesy of the firm.

The growth in broth was luxuriant and homogeneous, with a slight granular surface ring after forty-eight hours. There was no pellicle formation. Growth occurred readily on the these mediums and on simple extract agar at room temperature, but less luxuriantly than at 37.5 C.

Fermentation reactions were carried out at 37.5 C. in nutrient broth containing 1 per cent of the respective fermentable substances. The following results were obtained: Acid was produced in dextrose and maltose in twenty-four hours; mannitol was fermented in forty-eight hours, and, though growth was profuse in lactose, ramnose, sucrose, dulcitol and levulose broths, no acid was produced in sealed or unsealed tubes in twenty-eight days. Gelatin was not liquefied and litmus milk remained unchanged during the twenty-eight days of observation. The oxidase test revealed that the organisms were neisserian.

After three months' culture on various types of mediums, the colony characteristics were relatively unchanged. Capsule formation, however, was often absent.

The organism in a homogenous suspension in isotonic solution of sodium chloride was not agglutinated or altered by polyvalent or type-specific antimeningococcic serums obtained from a reputable commercial house, or by the serum from the Army Medical Department Research and Graduate School.

According to Topley and Wilson,[3a] D. mucosus was first isolated by von Lingelsheim from the nasopharyngeal and cerebrospinal fluids. It is characterized by its large capsule, the ability to develop on plain agar and at room temperatures and the formation of mucoid colonies. These authors stated that the systemic position of the organism is still in doubt, though it probably belongs to the genus Neisseria.

The organism isolated in this case exhibited the basic cultural and other characteristics ascribed to D. mucosus.

COMMENT

The case reported in this paper represents an unusually mild infection as compared with other types of meningitis seen in infancy and early childhood. The meningeal and constitutional reactions exhibited were milder than is usual in septic infections in patients of this age group. The infection responded rapidly to therapy with sulfadiazine and penicillin. It is possible that this patient would have recovered with sulfadiazine therapy alone, as the spinal fluid had already been freed of viable organisms. Penicillin therapy was instituted, however, because meningeal infections in infancy generally are extremely serious and difficult to control. Coincidental with penicillin therapy, there were an immediate drop of temperature to normal and apparent improvement in the general condition of the patient, while the blood became free of viable organisms.

Because in its early stages the infection was diagnosed as meningococcic, the use of specific serum complicated recovery by initiating serum sickness. This condition was controlled by the use of diphenhydramine hydrochloride. Hypersensitivity to sulfadiazine also made its appearance.

Several cases of infection with the D. mucosus in adults appear in the literature, but no case occurring in infancy has been reported.

Cowan [3b] isolated two strains of the organism from 2 cases of infection that developed after operation for cerebral tumor. One of these strains was isolated only at autopsy, and no evidence of meningitis was observed. McFarlan [3c] reported a case of purulent meningitis in a man aged 24 from whom this organism was isolated. This patient improved rapidly and made a complete recovery with sulfapyridine therapy. Bray and Cruickshank [3d] reported a relatively mild case of meningitis occurring in a 29 year old soldier. On lumbar puncture a turbid fluid was obtained, with a count of 330 cells per cubic millimeter, which were chiefly polymorphonuclear leukocytes. The protein in the spinal fluid was 240 mg. per hundred cubic centimeters. The spinal fluid in their patient showed both intracellular and extracellular diplococci, which were proved culturally to be D. mucosus.

SUMMARY AND CONCLUSIONS

A case of meningitis due to D. mucosus occurring in an infant, successfully treated with sulfadiazine and penicillin, is described. A review of the literature revealed only 5 cases of meningitis due to this organism—all cases hitherto reported have been those of adults.

The cultural characteristics of the organism isolated are shown to conform to those of D. mucosus.

The possibility of infection with D. mucosus should be considered in cases of atypical "meningococcic" meningitis.

Serum sickness, a complication of therapy with antimeningococcic serum, was controlled with administration of diphenhydramine hydrochloride ("benadryl hydrochloride").

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POTASSIUM BROMATE POISONING

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BROMIDE intoxication is well defined in its manifestations and represents a not uncommon clinical entity. Bromate poisoning is rare, however, and it is only briefly mentioned in textbooks of pharmacology and toxicology.[1] In contrast to the many investigations on the chlorates, experimental studies of bromate action are few.[2] A review of the literature reveals only 1 recorded instance of bromate poisoning in man.[3] The case reported here is of interest, accordingly, not only from the point of view of rarity but also as an instructive example of bromate toxicity which is distinct from the toxicity of a bromide salt.

REPORT OF A CASE

The patient, a 17 month old boy, was seen at the Children's Memorial Hospital on Sept. 9, 1946, four hours after swallowing an unknown quantity of a neutralizing solution for use on the hair after the application of a "cold wave" hair lotion. The child had vomited several times after ingesting the fluid but had appeared alert and well. Gastric lavage was performed, and he was later admitted to the hospital because of irritability, restlessness and vomiting. The physical findings were essentially normal except that the child was pale and appeared toxic and irritable. Oral intake of fluids was urged, and supplemental clyses of dextrose in isotonic solution of sodium chloride were administered. On September 11, the red cell count was 3,500,000; the hemoglobin content, 8.5 Gm. per hundred cubic centimeters, and the white cell count, 11,000, with a normal differential count. Examination of the urine revealed a p_H of 7.5, a 4 plus reaction for albumin and 6 to 8 red blood cells and an occasional white blood cell per high power field. Methemoglobinuria was not noted, and there was no evidence of methemoglobinemia.

There was some clinical improvement on September 11, followed by oliguria, tachypnea, listlessness and apathy on September 12, when the following chemical values of the blood were obtained: nonprotein nitrogen, 94 mg. and urea nitrogen 60 mg., per hundred cubic centimeters, and carbon dioxide-combining power, 25 volumes per cent. The neutralizer ingested, dispensed as a powder to be dissolved

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1. (*a*) Sollmann, T.: A Manual of Pharmacology and Its Applications to Pharmacology and Toxicology, ed. 2, Philadelphia, W. B. Saunders Company, 1922. (*b*) Cushny, A. R.: A Textbook of Pharmacology and Therapeutics, ed. 11, Philadelphia, Lea & Febiger, 1936. (*c*) Goodman, L., and Gilman, A.: The Pharmacological Basis of Therapeutics, New York, The Macmillan Company, 1941.

2. Santesson, C. G., and Wickberg, G.: The Action of Sodium Bromate, Skandinav. Arch. f. Physiol. **30**:337, 1913.

3. Carratala, R., and Urcaray, L.: Grave Intoxication Due to Ingestion of Potassium Bromate, Rev. Asoc. méd. argent. **55**:529, 1941.

in water before use, was reported by the manufacturer to consist of potassium bromate. The hair lotion proper contained thioglycolic acid in ammonia dispensed in an emulsifying solution. The patient had a generalized convulsion on September 13 and was stuporous and moderately edematous, with the edge of the liver palpable 3 fingerbreadths below the costal margin. There was oliguria, bordering on anuria, with nonprotein nitrogen of 103 mg. and urea nitrogen 82 mg., per hundred cubic centimeters, and carbon dioxide-combining power of 36.4 volumes per cent. Treatment consisted of administration of sixth-molar solution of sodium lactate, dextrose in distilled water intravenously, magnesium sulfate and phenobarbital. Convulsions increased in severity and number; edema became more pronounced and generalized; oliguria passed into anuria, and the patient died on September 10.

Autopsy.—The gross and microscopic descriptions are limited to significant observations.

Gross Examination: The body was that of a well developed white boy with severe generalized edema. Approximately 300 cc. of a clear fluid was observed in the abdominal cavity, and 150 to 200 cc. of a similar fluid was present in each pleural cavity. The heart weighed 72 Gm. (normal weight, 52 Gm.) and appeared pale and edematous. There was moderate dilatation of the right auricle and ventricle. The lungs weighed three times their expected weight and presented evidence of edema and congestion. The right kidney weighed 72 Gm. (normal weight, 40 Gm.) and the left kidney 70 Gm. (normal weight, 43 Gm.). Both kidneys were large, pale and edematous. The renal capsules were stripped with ease. Corticomedullary differentiation was indistinct. The cortex, which showed an increase in thickness, was pale and white. The medulla was light purple with indistinct markings. The bladder was empty but appeared normal. Except for moderate hyperemia of the gastric mucosa, the gastrointestinal tract was normal throughout.

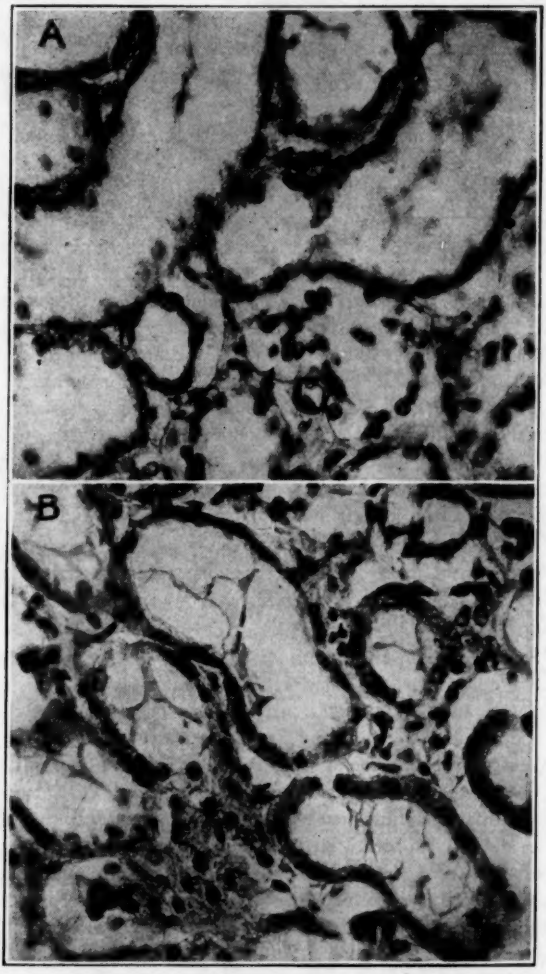
Microscopic Examination: Study of sections taken from all the abdominal viscera revealed that significant pathologic changes were limited to the kidneys, liver, heart and lungs.

Kidneys: Sections taken from both kidneys revealed an irritative and degenerative process confined to the tubules. The straight tubules in the medullary zone showed cloudy swelling, cellular necrosis and degeneration, with evidence of karyorrhexis and karyolysis. In many areas the spaces between the tubules were narrowed, with attendant compression of the peritubular glomeruli. Dilatation of the proximal convoluted tubules had resulted in a lining of flattened epithelium, and in areas of thin, persisting basal portions of cells. Multinucleated cells with hyperchromatic nuclei and occasional mitotic figures suggested an attempt at regeneration of the damaged tubular epithelium. Intratubular accumulation of desquamated epithelium and cellular debris occurred. The glomeruli showed no increase in cellularity, were relatively free of capillary blood, and lay in clear capsular spaces. A moderate interstitial infiltration of inflammatory cells, predominantly lymphocytic, was noted. Although the tubular damage described was diffuse, the structural changes did not seem of themselves to explain the entire clinical picture of anuria.

Liver: Involvement of the hepatic parenchyma was severe and diffuse. Swelling of the cells of the hepatic cords was prominent, with attendant narrowing and virtual obliteration in many areas of the sinusoidal spaces. Loss of cellular outline, karyorrhexis and karyolysis occurred. The hepatic cells had a washed-out appearance and contained a fine granular precipitate. Hepatic edema was mani-

fested by an accumulation of fluid between the hepatic cell cords and the walls of the sinusoids.

Heart: In sections taken from the heart, changes attending an acute toxic myocarditis had occurred. The muscle fibers showed a moderate degree of swelling and loss of cross striation. Many of the muscle fibers were fragmented transversely. Interstitial edema was prominent and was associated with an infiltration of moderate numbers of mononuclear cells, predominantly lymphocytic.



Sections of the kidney in a case of potassium bromate poisoning, showing flattening of the tubular epithelium, intratubular accumulation of desquamated epithelial cells, cellular necrosis, karyorrhexis and karyolysis.

Lungs: The sections showed vascular congestion, extravasation of red blood cells into the alveolar spaces, distention of the alveolar capillaries and transudation of an edema fluid into the alveoli. The lining of the bronchioles was intact. Plugging of the lumens of the bronchioles with inflammatory exudates did not occur.

COMMENT

The bromides are depressants of the central nervous system. Their activity depends on free bromide ions, whose effect bears no relation to the associated cations. Bromides are excreted almost exclusively in the urine in a manner similar to that of chlorides, there being only a slight renal preference for chloride excretion.[4] Bromide concentrations that depress the activity of the central nervous system have little effect on the kidneys or on other tissues of the body, which react similarly to chlorides and bromides. Bromates and other bromine-containing compound, such as bromoform (tribromomethane), "bromural" ([2-bromo-isovaleryl] urea) and bromal hydrate, which do not release the ionic form, however, do not possess the action typical of ionizable bromide salts.[1c]

The bromates react similarly to the chlorates. The chlorates are ordinarily not reduced in the body, 90 to 96 per cent of the amount administered being recovered from the urine.[1b] Symptoms of chlorate intoxication are referable to the gastritis, nephritis and formation of methemoglobin which attend an overdose of chlorate. Bromates are only partly reduced in the tissues,[1a] but they are twenty to thirty times as toxic for the experimental animal as are the chlorates.[2] Santesson and Wickberg's studies [2] indicated that sodium bromate was less toxic than the potassium salt, the potassium ion enhancing bromate toxicity. Potassium bromate was observed to depress the blood pressure, presumably by action on the vasomotor center. Symptoms of bromate poisoning in animals included apathy, increased salivation and vomiting, diarrhea and depression of the central nervous system, particularly the respiratory center. It was the investigators' opinion that diarrhea is prompted by a stimulating action of the bromates, increasing intestinal secretions. Formation of methemoglobin, observed in cases of chlorate poisoning, was not seen in dogs, rabbits or guinea pigs given toxic doses of potassium bromate, though hemolysis of the red blood cells occurred in the guinea pig. Conspicuous changes were observed in the kidneys of the dogs. Vascular congestion, intrarenal hemorrhage, desquamation of the epithelium and tubular degeneration, involving especially the ascending loops of Henle, were noted.

Attention recently has been called to poisoning occurring in connection with the "cold wave" process.[5] Severe allergic reactions, affecting chiefly the skin and mucous membranes, were related to sensitivity to thioglycolic acid, the active constituent in "cold wave" hair lotions. The case recorded here directs attention to the toxicity of a neutralizing solution used on the hair after the lotion has been applied and the wave "set." While the acid may be washed off with hydrogen peroxide or water with impunity, a bromate neutralizer used for such a purpose is potentially dangerous, as in the present case.

The renal lesions in this case were primarily tubular. While diffuse, they did not appear of such severity as to explain the entire clinical picture of anuria. Primary hepatic edema of the type described by

4. Hastings, A. B.; Harkins, H. N., and Lin, S. K.: Blood and Urine Studies Following Bromide Ingestion, J. Biol. Chem. **94**:681, 1932.

5. Cotter, L. H.: Thioglycolic Acid Poisoning in the "Cold Wave" Process, J. A. M. A. **131**:592 (June 15) 1946.

Keschner and Klemperer [6] and interpreted as morphologic evidence of increased permeability of the capillary wall was noted. A similar increase in systemic capillary permeability due to the ingested chemical toxin, with a corresponding prerenal deviation of fluid, may have occurred. Richards and Wearn [7] reported that complete cessation of formation of urine may follow the administration of a tubular poison. Water and other substances pass back into the blood by a simple process of diffusion, though the specific reabsorptive processes may be abolished. A reduction in urinary volume may result, however, not only from an increase in the rate of tubular diffusion but also from a decrease in the rate of glomerular filtration, or from a combination of the two factors. Evidence of acute toxic myocarditis, which may be produced by renal irritants,[8] was seen in microscopic sections of the heart. It is possible that a toxic myocarditis, together with the central depression of the vasomotor center, as observed by Santesson and Wickberg,[2] may also have contributed to the showing of the rate of glomerular filtration, with a reduction in urinary secretion. The rapid onset of the edema makes it seem unlikely that hypoproteinemia, with a reduction in colloid osmotic pressure, played a prominent role. Whatever the cause of the anuria, the changes were irreversible and death ensued early.

It is somewhat redundant to suggest that adequate precautions in labeling are essential in dispensing potentially toxic agents. It would appear more pertinent, however, to indicate that the continued use of potassium bromate in the "cold wave" process represents an unnecessary hazard, for either hydrogen peroxide or water is adequate for the same purpose.

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6. Keschner, H. W., and Klemperer, P.: Frequency and Significance of Hepatic Edema, Arch. Path. **22**:583 (Nov.) 1936.

7. Richards, A. N., and Wearn, J. I.: Problem of Reabsorption in the Renal Tubules, Am. J. Physiol. **71**:209, 1924. Richards, A. N.: Methods and Results of Direct Investigation of Function of the Kidney, in Harvey Lectures, Baltimore, Williams & Wilkins Company, 1934, vol. 30, p. 93.

8. Christian, H. A.; Smith, R. M., and Walker, I. C.: Experimental Cardiorenal Disease, Arch. Int. Med. **8**:468 (Oct.) 1911.

Abstracts from Current Literature

Metabolism; Infant Feeding; Milk and Other Foods

STUDIES ON THE COMPARATIVE NUTRITIVE VALUE OF FATS: VIII. THE FAILURE OF ETHER EXTRACTION TO LOWER THE NUTRITIVE VALUE OF SKIMMED MILK POWDER IN DIETS CONTAINING VARIOUS VEGETABLE FATS. HARRY J. DEUEL JR., CORNELIA HENDRICK, ELI MOVITT, MARY E. CROCKETT, IRENE M. SMYTH and RICHARD J. WINZLER, J. Nutrition **31**:747 (June) 1946.

The authors observed no differences in rate of growth or in the ultimate total gain in weight over a twelve week period of observation, during which weanling male or female rats were fed extracted skimmed milk powder mixed with fat, irrespective of whether a butter or a margarine or corn, cottonseed, peanut or soybean oil was the fat used.

FREDEEN, Kansas City, Mo.

STUDIES ON THE COMPARATIVE NUTRITIVE VALUE OF FATS: IX. THE DIGESTIBILITY OF MARGARINE FAT IN HUMAN SUBJECTS. HARRY J. DEUEL JR., J. Nutrition **32**:69 (July) 1946.

The author reports that margarine fat from a commercial margarine composed of hydrogenated domestic vegetable oils was digested by normal men and women to an average of 97 per cent, which was the value obtained in three tests on butter fat.

FREDEEN, Kansas City, Mo.

METABOLISM OF VITAMIN D: III. DETERMINATION OF DAILY NEED OF THE VITAMIN IN BABIES. RENÉ HOUET, Ann. pædiat. **167**:225 (Nov.) 1946.

When increasing doses of vitamin D are added to the routine diet of sucklings, the intestinal absorption of calcium and phosphorus is at first improved, and then reaches a level that cannot be improved even by the administration of a larger quantity of the vitamin.

Similarly, the urinary output of calcium and phosphorus reaches a level which cannot be increased even by higher physiologic levels of the vitamin.

The ratio of fecal to urinary phosphorus (fecal P/urinary P $= \pm 0.5$) is a sensitive test of avitaminosis D in sucklings. Unfortunately, the test is not a practical one for sucklings and children, since it is difficult to collect all the urine passed by these subjects.

The daily amount required by sucklings to prevent avitaminosis D is about 250 units when given as activated 7-hydroxycholesterol (vitamin D_3) in an oily solution.

FROM THE AUTHOR'S SUMMARY.

CALCIUM AND PHOSPHORUS METABOLISM IN CHILDREN: IV. DURATION OF ACTION OF A SINGLE DOSE OF FIFTEEN MILLIGRAMS VITAMIN D IN THE RACHITIC INFANT. RENÉ HOUET, Ann. paediat. **167**:235 (Nov.) 1946.

When a dose of 15 mg. of vitamin D is given a nursing infant with rickets, better phosphorus and calcium absorption occurs, which may last two or three, or sometimes four, months. Thus, it would seem that administration of a dose of 15 mg. of vitamin D three times a year would keep an infant free from rickets.

The sudden rise in the urinary output of calcium and phosphorus seen as a rule after a dose of 15 mg. is transitory, in striking contrast to the lasting improvement in the intestinal absorption of these mineral salts.

There is also a striking difference in the daily requirements of vitamin D, depending on whether the vitamin D is given as a single massive dose or in the form of daily drops.

FROM THE AUTHOR'S SUMMARY.

Vitamins; Avitaminoses

THE RETENTION OF NUTRIENTS IN CHEESE MAKING: IV. THIAMINE IN CHEDDAR CHEESE MADE FROM RAW AND PASTEURIZED MILK. E. V. EVANS, O. R. IRVINE and L. R. BRYANT, J. Nutrition **32**:227 (Sept. 10) 1946.

The fate of thiamine in the manufacture of Cheddar cheese and the effect of the ripening periods up to twelve months on this vitamin in the cheese produced were studied by the authors. Pasteurized milk showed little or no loss of thiamine. A progressive decrease in thiamine content of the cheese with the increasing ripening period was observed. The losses in twelve months ranged from 43 to 73 per cent.

FREDEEN, Kansas City, Mo.

PHARMACOLOGIC STUDIES WITH VITAMIN B_6 [PYRIDOXINE]. L. NASSI, Riv. di clin. pediat. **41**:457 (Sept.) 1943.

The author observed the action of pyridoxine on the isolated hearts of frogs and guinea pigs and on the intestinal mobility, ear capillaries, arterial blood pressure, pulse rate and respiration of rabbits. He concludes that pyridoxine has a mild parasympathetic action on the vegetative nervous system, similar to that of epinephrine.

HIGGINS, Boston.

Prematurity and Congenital Deformities

THE USE OF NORMAL SERUM GAMMA GLOBULIN ANTIBODIES (HUMAN) CONCENTRATED (IMMUNE SERUM GLOBULIN) IN THE TREATMENT OF PREMATURE INFANTS. LEWIS K. SWEET, M. JANE HOWELL, LUCY-GALE MCMURRAY, WILLIAM A. MCMAIN JR., and GUNNARD J. ANTELL, J. Pediat. **28**:571 (May) 1946.

Gamma globulin, in doses of 2.5 cc. (equivalent to the gamma globulin from 62.5 cc. of normal pooled human plasma), given on the second, eighth and fifteenth days of life and thereafter every two weeks until a weight at discharge of 5 pounds 8 ounces (2,500 Gm.) was reached, was administered to 117 prematurely born infants; 113 infants of similar birth weight who received no gamma globulin were studied as control patients. There was no difference in the gross mortality and morbidity rates for the two groups of infants. Likewise, there was no significant difference in the time required for the two groups of infants to regain the birth weight or to attain a weight at discharge of 5 pounds 8 ounces.

FROM THE AUTHORS' SUMMARY.

DEVELOPMENT FACTOR IN RELATIONSHIP OF CONGENITAL DISTURBANCES OF THE RHINENCEPHALON, ADRENAL GLANDS AND GENITALIA. BENNO GRÜNFELDER and W. LASCH, Ann. pædiat. **167**:254 (Nov.) 1946.

The development of the rhinencephalon, the adrenal glands and the genital organs starts simultaneously during the fifth and sixth weeks of pregnancy. Damage

occurring to the fetus shortly before and during this period will produce malformations in the three systems of organs: aplasia or hypoplasia of the olfactory nerve, aplasia or hypoplasia of the adrenal glands, hypoplasia of the testes or ovaries, cryptorchism, uterus bicornis and anomalies of the scrotum, urethra and vulva.

Sometimes only two of the systems mentioned, the rhinencephalon and the adrenal glands or the rhinencephalon and the genital organs, are affected by the damage.

FROM THE AUTHORS' SUMMARY.

Newborn

HEMOLYSIS FROM IRREGULAR ISOAGGLUTININS (COLD AGGLUTININS) FOLLOWING TREATMENT FOR ERYTHROBLASTOSIS FETALIS. HEYWORTH N. SANFORD and JESSE R. GERSTLEY, J. Pediat. **28**:574 (May) 1946.

An infant with erythroblastosis neonatorum received transfusions from five donors of the same blood group, of both Rh-negative and Rh-positive blood. An intense hemolysis resulted from cold agglutinins in the infant's blood, which reacted on the blood of these five donors. Recovery took place immediately after the blood of two other Rh-positive donors was given that was not hemolyzed by the infant's cold agglutinins.

The infant recovered completely after receiving twenty-two transfusions, or a total of 2,300 cc. of blood, over a period of thirty-three days. During this period the infant's icterus index rose to 470 and remained at this point for eleven days. This did not cause kernicterus or harm the child in any way.

FROM THE AUTHORS' SUMMARY.

PROBLEMS IN PREVENTING INFECTIONS IN NEWBORN NURSERIES. SAMUEL FRANT, HAROLD ABRAMSON and MARGARET LOSTY, New York State J. Med. **46**:908 (April 15) 1946.

With the overcrowding that has taken place in maternity hospitals, there is still more demand that scrupulous attention be given to well defined details of nursery technic. A sanitary code of the city of New York was the first to contain provisions for the conduct and maintenance of neonatal and maternity services. A supplementary report on standards and recommendations for maternity hospitals has recently been drawn up. This report was approved by obstetricians, pediatricians, nursing educators and health administrators and by the Advisory Obstetric Council of the New York State Department of Health. These rules are based on fundamental principles that are recognized by all epidemiologists as necessary for the prevention of communicable conditions, and are summarized as follows:

1. The physical plant must be properly designed and maintained. The department of obstetric and neonatal care should be a distinct unit. Gynecologic and pediatric services should be completely divorced from maternity services. Special attention should be given to plumbing hazards to prevent back siphonage and infection of the water supply.

2. An adequately trained personnel is essential. The New York State Department of Health has arranged for nurses to attend refresher courses in the teaching institutions. Everyone assigned to maternity and newborn infant services should be examined and certified as free from communicable disease. Roentgenographic examination of the chest is essential.

3. A distinction should be drawn between the care of "clean," or uninfected, maternity patients and their babies and the care of those ill and infected. The latter should be cared for by a separate obstetric personnel. It is even recommended that a "suspect nursery" be maintained where children may be placed until the question of infection is decided.

4. Complete aseptic technic should be observed in the care of infants. The trend is toward the breaking up of large maternity wards and nurseries of the dormitory type into smaller units, where individualized care may be given. Common dressing tables and sink slabs for bathing should be eliminated.

5. Formulas should be prepared in the obstetric department for newborn children only, and not for infants in the pediatric services.

6. If the hospital is unable to provide complete special service for premature children, such patients should be removed to other institutions where experienced personnel is available.

AIKMAN, Rochester, N. Y.

COMPLICATIONS OF BLOOD TRANSFUSIONS DUE TO THE RH FACTOR. G. A. J. DUNSELMAN, Nederl. tijdschr. v. geneesk. **90**:964 (Aug. 10) 1946.

The author describes 2 cases in which blood transfusions were followed with complications in which the Rh factor played a part. In 1 case, which ended fatally, (uremia and anuria) the transfusion was given a patient who had just given birth to a child with hydrops fetalis. The changes observed in the kidneys of this patient are described.

VAN CREVELD, Amsterdam, the Netherlands.

Acute Contagious Diseases

OBSERVATIONS MADE DURING A POLIOMYELITIS EPIDEMIC IN 1944 IN THE HORNELL STATE HEALTH DISTRICT, NEW YORK. JOHN A. CONWAY and D. E. BIGWOOD JR., New York State J. Med. **46**:275 (Feb. 1) 1946.

This report concerns the poliomyelitis epidemic which occurred in 1944 in the three counties comprising the Hornell District of the New York State Department of Health.

The epidemic was unique in the area involved and of unusual severity. In the three counties of Allegany, Steuben and Chemung 591 cases occurred among a population of about 200,000.

This epidemic showed no clearcut evidence of spread of the disease from one member to another in families. In this experience, previous contacts with persons with the disease could be interpreted as a matter of chance. The possibility of an insect vector as an agent in the spread of poliomyelitis is suggested by the seasonal incidence of the disease.

The study is accompanied with maps and charts. It is urged that a virus laboratory be set up. (Such laboratory facilities have since been provided by the New York State Board of Health.)

AIKMAN, Rochester, N. Y.

A REPORT ON POLIOMYELITIS CASES FROM THE HOSPITAL FOR SPECIAL SURGERY OF NEW YORK CITY. K. G. HANSSON and L. RAMSAY STRAUB, New York State J. Med. **46**:1009 (May 1) 1946.

This report is a general survey of 158 patients with poliomyelitis treated at the Hospital for Special Surgery, New York city, in 1944. The authors suggest the great need for the establishment of a hospital for poliomyelitis patients in close

association with an active orthopedic hospital, for a summer camp for poliomyelitis patients and for the development of a new type of brace.

AIKMAN, Rochester, N. Y.

Acute Infectious Diseases

INFANTILE TOXOPLASMOSIS. A. GALDO VILLEGAS, Rev. españ. de pediat. **2**:149 (March-April) 1946.

The author reviews the literature on infantile toxoplasmosis and gives a general discussion of the disease. He has not seen a case which he recognized but recalls cases which might have been of this nature. He points out that the disease is widely distributed in animals, having been reported in Europe—in England, France and Germany. The occurrence of cases in human beings has been proved only in the United States, but probable cases published prior to the discovery of the cause have appeared in the literature of the Netherlands and Czechoslovakia. No cases have been discovered in Spain in either animals or human beings, but, in the author's opinion, cases would be reported if the disease were generally recognized when seen.

MILLER, Newark, Ohio.

SUBSEPSIS ALLERGICA (WISSLER): REPORT OF A CASE. G. FANCONI, Helvet. pædiat. acta **1**:532 (Oct.) 1946.

The diagnosis of subsepsis allergica (Wissler) was made in the case of a 7 year old boy, since he had intermittent fever and a recurring exanthem which was at one time urticarial and at another scarlatiniform, or resembling erythema annulare Leiner. The blood often presented neutrophilic leukocytosis, with the eosinophil count maintained or even increased. Rheumatoid pains were frequently felt in the joints. The spleen was not, or was only barely, palpable. Cultures of the blood were always sterile. In the "spectrum" of bacterial diseases, subsepsis allergica falls between true rheumatism and chronic polyarthritis.

FROM THE AUTHOR'S SUMMARY.

Chronic Infectious Diseases

ANTI-TUBERCULOSIS VACCINATION. IRWIN S. NEIMAN, Illinois M. J. **90**:131 (Aug.) 1946.

In the opinion of the author, of all the various types of immunizing agents which have been used for the purpose of preventing tuberculosis, the one which has offered the greatest degree of promise has been BCG. Objections which have been offered to its general use are not of a nature to warrant its condemnation. The vaccine should be made available certainly to children in families in which there are known cases of tuberculosis, to children who live in highly tuberculous environments, even though there is no known tuberculosis in the family and voluntarily to all others. In addition, it should be made available to adults whose occupation necessarily exposes them to tuberculosis, primarily, nurses and medical students.

BARBOUR, Peoria, Ill.

PENICILLIN IN THE TREATMENT OF SYPHILIS IN CHILDREN. JOSEPH YAMPOLSKY and ALBERT HEYMAN, J. A. M. A. **132**:368 (Oct. 19) 1946.

Sixty-one children with various manifestations of syphilitic infection were treated with penicillin. The drug appears to be an effective agent in the treatment

of infantile congenital syphilis, and satisfactory results were obtained in 23 of 32 children treated for this condition.

For the majority of patients with interstitial keratitis parenteral administration of penicillin did not give satisfactory results, and the drug was also of little value in the treatment of Clutton's hydrarthrosis (Clutton's joint). Acquired syphilis in children seemed to respond readily to doses of penicillin comparable to those used for adults. The changes in the spinal fluid in cases of late congenital asymptomatic neurosyphilis were in general satisfactory and comparable to those obtained with fever therapy. Little or no clinical improvement was noted in patients with juvenile dementia paralytica treated with penicillin. One patient with mild eighth nerve deafness obtained improvement in hearing after receiving penicillin.

In general, the results obtained with penicillin in the treatment of syphilis in children seem to depend on the nature and duration of the disease. Although penicillin appears to be effective in the treatment of infantile congenital syphilis and of early neurosyphilis, little or no response can be expected in the treatment of the late manifestations of this disease. FROM THE AUTHORS' SUMMARY.

TUBERCULOUS MENINGITIS TREATED WITH STREPTOMYCIN. L. L. KRAFCHIK, J. A. M. A. **132**:375 (Oct. 19) 1946.

A case of tuberculous meningitis in a 15 month old child is presented. Streptomycin therapy was begun two weeks after the onset of acute symptoms. The spinal fluid at that time showed a sugar content of 15 mg. per hundred cubic centimeters, and acid-fast bacilli were observed on direct smear of the pellicle. Streptomycin therapy was given for fifty-seven days except for a two day period after the thirty-second day, when the drug was not obtainable. The child received 24,000,000 units intramuscularly and 2,800,000 units intrathecally, in sixty-five spinal taps.

The patient was discharged two months after therapy was instituted, although slight fever persisted another month. The spinal tap four months after institution of streptomycin therapy showed only 140 cells, mostly lymphocytes, and a sugar content of 66 mg. per hundred cubic centimeters. At the time of the report, five months after the onset of his illness, the child is clinically well, afebrile and mentally normal.

BAIRD, Wauwatosa, Wis.

ALLERGOMETRIC STUDIES OF TUBERCULOUS CHILDREN. CATERINA FONTANA, Riv. di clin. pediat. **41**:46 (Jan.) 1943.

In tuberculous children with infiltrative lesions or with hyperplastic glands, a reaction to tuberculin will occur in a weak concentration; as the pathologic condition regresses, the reaction appears only with stronger concentration of tuberculin.

HIGGINS, Boston.

Diseases of Blood, Heart and Blood Vessels and Spleen

THE ANEMIA OF INFECTION: IV. THE LACK OF RELATIONSHIP BETWEEN THE DIVERSION OF IRON FROM THE PLASMA AND THE ORIGIN OF THE ANEMIA. G. R. GREENBERG, HELEN ASHENBRUCKER, MARJORIE LAURITSEN and M. M. WINTROBE, J. Clin. Investigation **26**:114 (Jan.) 1947.

Persistent hypoferremia exists in cases of chronic infection. When iron is administered intravenously in such cases, it is rapidly removed from the plasma.

The authors undertook to determine whether, by raising the iron level to a normal value, the synthesis of hemoglobin could be induced in cases of anemia with chronic infection.

Intravenous infusions of iron for periods as long as seventy-two hours were given to patients. Considerably more iron was required to maintain a normal iron level in the plasma than would be expected. This was explained by a powerful braking mechanism which acts to prevent the iron in the plasma from exceeding certain limits. Despite this barrier, it was possible to raise the iron level of the plasma temporarily (seventy-two hours). However, no increase in the synthesis of hemoglobin occurred, as shown by determination of total circulating hemoglobin. It was also shown by using radioactive iron that small amounts of iron can be utilized in hemoglobin synthesis despite the presence of infection. This small iron uptake was explained by the appearance of new erythrocytes containing hemoglobin to replace those which had become worn out in the course of time. The authors concluded that since intensive iron therapy was ineffective in their cases, iron deficiency is not the cause of anemia of infection, despite diversion of iron from the plasma.

BRODSKY, Cincinnati.

THE ANEMIA OF INFECTION: V. FATE OF INJECTED RADIOACTIVE IRON IN THE PRESENCE OF INFLAMMATION. G. R. GREENBERG, HELEN ASHENBRUCKER, MARJORIE LAURITSEN, WANDA WORTH, S. R. HUMPHREYS and M. M. WINTROBE, J Clin. Investigation **26**:121 (Jan.) 1947.

Radioactive iron was injected intravenously into normal rats and into rats with an acute inflammatory process. The data obtained indicated that in the presence of infection a significant proportion of radioactive iron is not diverted away from the organs usually engaged in iron metabolism; namely, the liver, spleen and erythrocytes. Control rats showed better iron uptake by the red cells than did those with inflammation. However, the rats subjected to inflammation usually had more Fe^{59} in the liver than did the controls. No significant quantities of injected iron were observed in the inflamed area or in the excreta. The authors concluded that in cases of infection the major diversion of iron from the plasma is to the liver and that this diversion is related to the hypoferremia observed. Since deficiencies of iron protoporphyrin and copper have been eliminated as factors in the genesis of anemia of infection, the protein moiety of hemoglobin was suspected as the significant factor.

BRODSKY, Cincinnati.

MEDITERRANEAN ANEMIA (COOLEY) IN A NEGRO GIRL. HAROLD K. FABER and BERNARD M. ROTH, J. Pediat. **28**:610 (May) 1946.

A girl aged 6 years, whose parents were known to be Negroes, had had recurrent epistaxis for three years. The only notable abnormalities in physical status were pallor of the mucous membranes, slight generalized lymphadenopathy, a soft systolic murmur, enlargement of the liver 4 cm. below the costal margin, enlargement of the spleen below the umbilicus and umbilical hernia. The blood count was as follows: red blood cells, 3,700,000; hemoglobin, 8.4 Gm. per hundred cubic centimeters (49 per cent Sahli), and leukocytes, 7,500 (neutrophils, 63 per cent; basophils, 3 per cent; lymphocytes, 26 per cent; plasma cells, 2 per cent, and monocytes, 6 per cent). There were 73 nucleated red cells per hundred leukocytes. The red cells were typical of Cooley's anemia, showing extreme poikilocytosis, anisocytosis and anisochromia, with target cells, pessary forms and other immature cells. The icterus index was 8. The packed cell volume was 30 cc. per thousand

cubic centimeters of blood; the mean corpuscular hemoglobin, 25.2 micromilligrams; the mean corpuscular volume, 72 cubic microns; and the mean corpuscular hemoglobin concentration, 32 per cent. The platelets numbered 260,000 per cubic millimeter. Erythrocytic fragility was normal. Repeated tests for sickling gave uniformly negative results. The Wassermann and Hinton tests gave negative reactions. Roentgenographic examination showed coarsening of the bony trabeculae in many bones, but not in the skull. A photomicrograph of the blood accompanies the paper.

AUTHORS' ABSTRACT.

CONGENITAL HEMOLYTIC DISEASE AND ERYTHROBLASTOSIS FETALIS: TWO DISEASE SYNDROMES. ALEXANDER S. WEINER, New York State J. Med. **46**:912 (April 15) 1946.

Persons sensitized to agglutinogens, such as Rh, A, B and Hr, may form two sorts of antibodies, the agglutinins (bivalent antibodies) and the blocking antibodies, or glutinins (univalent antibodies). The clinical manifestations depend on which variety of antibody is present in the maternal serum; therefore, according to the author, erythroblastosis fetalis actually comprises two clinical syndromes, instead of only one.

When the maternal serum contains univalent isoantibodies (blockers or glutinins), congenital hemolytic disease with anemia or hydrops may occur, or the two conditions may occur together. If only a small amount of the glutinins is present in the maternal serum, the child is usually born alive, with anemia, or acquires anemia shortly thereafter. When larger quantities are present, the condition progresses further into intrauterine life and hydrops occurs. In the other syndrome, it is believed that the agglutinins (bivalent antibodies) are larger molecules than the blocking antibodies and that agglutination thrombi occur in the smaller vessels, resulting in damage to such organs as the liver and brain. At this point erythroblastosis (with icterus gravis and kernicterus) occurs.

The statement that modern transfusion therapy may save these children for a worse fate of mental deficiency is misleading, for the author has reported that all infants (approximately 20 to date) saved by such treatment have become entirely normal children.

AIKMAN, Rochester, N. Y.

SPLENECTOMY: REPORT OF A CASE. A. INGUILLA, Riv. di clin. pediat. **40**:129 (March) 1942.

A boy, aged 7 years, had had jaundice, enlarged spleen and anemia, with a red cell count under 1,750,000, for three years. Within three months after splenectomy, the blood count had returned to normal and clinical recovery had been established.

HIGGINS, Boston.

DETERMINATION OF HEMOGLYCOLYSIS IN CHILDREN. E. COSSANDI, Riv. di clin. pediat. **41**:265 (May) 1943.

Sterile blood will show a gradual decline in its sugar content, owing to enzymatic glycolysis. The higher the granular leukocyte count of the blood, the greater the glycolysis. The author's method involves adding the fresh blood to a solution of sodium citrate. Determinations of the blood sugar are made before and after the blood has been in an incubator for two hours at 37 C. The results are expressed as milligrams of sugar undergoing glycolysis per hour per cubic centimeter of blood.

HIGGINS, Boston.

BLOOD LIPASE IN PREMATURE AND IN FULL TERM INFANTS. D. V. BORI, Riv. di clin. pediat. **41**:369 (July) 1943.

The blood lipase level was found to be as high in premature infants as in the infant born at term. The percentage of lipase, it was found, does not vary with the weight of the child.

HIGGINS, Boston.

LIBMAN-SACKS SYNDROME: REPORT OF A CASE. HANNA TOBLER, Helvet. pædiat. acta **1**:515 (Oct.) 1946.

A case of the Libman-Sacks syndrome in a girl 9 years of age is described and the differential diagnosis discussed. The disease followed the extraction of carious teeth. In addition to the general symptoms, necrosis due to arteritic changes was of the chief clinical interest. Endocarditis was not present. The disease is classified with focal infections between endocarditis lenta and periarteritis nodosa.

FROM THE AUTHOR'S SUMMARY.

ATYPICAL VERRUCOUS ENDOCARDITIS WITH CUTANEOUS AND VASCULAR MANIFESTATIONS (LIBMAN-SACKS SYNDROME): REPORT OF A CASE. SONJA BUCKLEY, Helvet. pædiat. acta **1**:524 (Oct.) 1946.

A case of the Libman-Sacks syndrome in a girl aged 10 years is reported. The clinical features were severe trophoneurotic changes in the skin, unclear pneumonopathy, chronic nephropathy (albuminuria, erythrocyturia, cylindruria), chronic leukopenia, sterile blood cultures and enlargement of the spleen and lymph nodes.

Anatomic examination showed atypical verrucous endocarditis (Libman) with a maximum of changes on the right side of the heart (tricuspid valve). This change constituted an important factor in diagnosis (Gross). Bacterioscopic examination of the lesions of the valves revealed no pathogens; Ashchoff nodules were absent. Numerous organs (kidney, stomach, brain, skin, tongue, spleen and myocardium) showed changes similar to those of periarteritis nodosa. The kidney presented also the picture of a nonpurulent focal nephritis (type Löhlein).

The Libman-Sacks syndrome is thought to be the sequel of a chronic focal infection. It is probably a link between rheumatic endocarditis and endocarditis lenta (von Albertini), with a greater resemblance to the latter.

FROM THE AUTHOR'S SUMMARY.

ESSENTIAL THROMBOPENIA: REPORT OF A CASE OF ITS EVOLUTION DURING THREE AND ONE-HALF YEARS FOLLOWING SPLENECTOMY COMPLICATED WITH AN ATTACK OF MALARIA. ASIM ISTANBULLU, Ann. pædiat. **167**:244 (Nov.) 1946.

In a case of essential thrombopenia, splenectomy had to be performed during the acute stage because the child's life was endangered, but this intervention stopped the hemorrhages for only fourteen months. Then the bleeding started again, but complicated with malarial attacks, during which an interesting lymphocytosis was observed. To what degree this lymphocytosis is connected with the hemorrhages should be more closely investigated. From the thirtieth month after the operation up to the time of the report, a period of nine months, no further clinical manifestations of essential thrombopenia were observed.

FROM THE AUTHOR'S SUMMARY.

Diseases of Nose, Throat and Ear

SPEECH COMES TO A FIVE YEAR OLD BOY. RUTH BECKEY IRWIN. J. Speech Disorders **11**:197, 1946.

A boy 5 years old, apparently normal physically and mentally, did not speak except for the word "mama," but used grunts and gestures for communicating ideas. The mother had been extremely nervous during the child's early life. The parents and grandparents discussed the boy's inability to talk in his presence. The child's needs were anticipated by associates. The mother had used bribes, ridicule, praise and punishment with the child. The author states that for several weeks no attempt was made to secure speech responses, but play therapy was given. A "Charley McCarthy" doll was used while confidence was developed. Blowing exercises were utilized. The mother was instructed not to pay attention to his grunts and unrecognizable speech sounds. A system of constant rewards was used as phonetic drill was begun, and efforts to produce speech sounds were attempted, with success At the end of eight months he made a score of 106 on a Stanford-Binet intelligence test, and at the last session, eight months after the first trip to the speech therapy office, he was talking spontaneously.

PALMER, Wichita, Kan.

Diseases of Lungs, Pleura and Mediastinum

TREATMENT OF BRONCHIAL ASTHMA WITH SMALL AMOUNTS OF COPPER. F. W. KLAARENBEEK, Nederl. tijdschr. v. geneesk. **90**:730 (June 29) 1946.

In 1945 the author described favorable results obtained in treating patients with bronchial asthma by means of intravenous injections of small amounts of a preparation of copper. Especially in young patients were the results favorable. In this article the author reports the results obtained in a new series, of 7 patients.

VAN CREVELD, Amsterdam, the Netherlands.

CYSTS AND TUMORS OF THE MEDIASTINUM. L. D. EERLAND, Nederl. tijdschr. v. geneesk. **90**:1252 (Sept. 28) 1946.

The author discusses the symptomatology and differential diagnoses of various cysts and tumors of the mediastinum, at the same time describing 2 cases in which thoracotomy was performed because of a teratodermoid of the mediastinum. The author points out the necessity of performing thoracotomy in every case in which a complete examination does not give a definite diagnosis as to the nature of the shadow observed on the roentgenogram.

VAN CREVELD, Amsterdam, the Netherlands.

INTRATHORACIC NEUROGENIC TUMORS. L. D. EERLAND, Nederl. tijdschr. v. geneesk. **90**:1257 (Sept. 28) 1946.

The author describes the symptoms of intrathoracic neurogenic tumors in 2 cases, in 1 of which there was an intrathoracic and cervical localization. If the diagnosis seems uncertain after a complete examination, a thoracotomy should be performed, unless there is a particular contraindication, and the tumor should be removed. This same procedure should be carried out even if no symptoms make intervention imperative and there is only a so-called "silent" tumor of the thorax.

VAN CREVELD, Amsterdam, The Netherlands.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

BIOLOGIC AND PATHOLOGIC SIGNIFICANCE OF YEASTS IN THE HUMAN INTESTINAL TRACT. F. COLONNELLO, Riv. di clin. pediat. **41**:472 (Sept.) 1943.

The author cultured for fungi the stools of 18 children with intestinal disturbances, none of the usual pathogenic bacteria having been observed previously. Torulas of various types were observed in the stools of 7 children; these organisms were also seen in the stools of 8 adults with amebic dysentery and in the stools of 6 healthy persons. The significance of these observations is difficult to evaluate. A similar condition is common in persons with sprue. One cannot tell definitely whether the molds and yeasts cause the pathologic condition or whether they are merely growing on unhealthy tissue, diseased from some other cause.

HIGGINS, Boston.

ANOREXIA, PARTICULARLY ANOREXIA NERVOSA, IN NURSING CHILDREN. S. LEVI, Riv. di clin. pediat. **44**:281 (May) 1946.

In camps for civilian refugees in Switzerland, a type of anorexia based on psychologic disturbances was observed in infants.

HIGGINS, Boston.

Nervous Diseases

THE TREATMENT OF EPILEPSY WITH A NEW DRUG: PHENANTOIN. HENRY L. KOZOL, Am. J. Psychiat. **103**:154 (Sept.) 1946.

"Phenantoin" ("mesantoin" [methyl phenylethyl hydantoin]) was used in treatment of 104 epileptic patients at Boston City Hospital. In 60 per cent the average monthly attacks were reduced to one-tenth their incidence before this drug was used—a reduction of 90 per cent in the frequency of attacks.

The maximum length of time between attacks was tripled. Thirty per cent of the patients remained free from attacks over a period of three to twenty-two months.

JAHR, Omaha.

HEMOPHILUS INFLUENZAE MENINGITIS TREATED WITH STREPTOMYCIN. HATTIE E. ALEXANDER, GRACE LEIDY, GEOFFREY RAKE and RICHARD DONOVICK, J. A. M. A. **132**:434 (Oct. 26) 1946.

A report on 25 patients who received streptomycin therapy is given. The dose of the drug was 20,000 units per pound (0.5 Kg.) of body weight per twenty-four hours given intramuscularly, and 25,000 to 50,000 units daily given intrathecally. Two patients showed reactions (coma) to an injection of the drug intrathecally, probably because of the presence of impurities. One child had damage to the eighth nerve, resulting in deafness.

Twelve of the patients had mild or moderately severe forms of the disease. All had received sulfadiazine therapy and had been ill less than eight days. All recovered with streptomycin alone. Five patients had a severer form of the disease or had been ill longer. These patients did not respond to streptomycin alone. One recovered and 2 lived after sulfadiazine and rabbit serum therapy. Four patients who had not responded well to sulfadiazine and serum therapy were given streptomycin. Two recovered and 1 lived. Four children were given treatment with all three therapeutic agents and all recovered.

The therapeutic results suggest that it is the severity of infection, and therefore the size of the bacterial population, which determines whether the strain of

organisms from a given patient will become resistant to streptomycin. Initial use of all three agents would probably reduce therapeutic failure to a minimum in cases of severe infections.

BAIRD, Wauwatosa, Wis.

MENINGITIS DUE TO ESCHERICHIA COLI: STREPTOMYCIN THERAPY. WILLIAM P. SHIELDS, J. A. M. A. **132**:514 (Nov. 2) 1946.

A case of meningitis due to Escherichia coli communior in a 5 week old child is reported. Sulfadiazine and penicillin therapy was instituted on the fifth day of apparent illness. Streptomycin therapy was begun two days later and continued for ten days. Administration was intramuscular and intracisternal. The child received 2,630,000 units intramuscularly and 300,000 units intrathecally, without apparent untoward reaction. Recovery was complete.

BAIRD, Wauwatosa, Wis.

NEURITIS FOLLOWING QUINACRINE THERAPY. S. MAGGIORE, Riv. di clin. pediat. **40**:179 (March) 1942.

A child 10 years of age with aestivoautumnal malaria did not respond satisfactorily to quinine therapy; therefore quinacrine hydrochloride "atabrine" (0.3 Gm. daily for ten days) was given, freeing the visible parasites which eliminated the blood. However, on the third day after the treatment was completed, a neuritis developed, involving the median and musculocutaneous nerves of the left arm. Intensive therapy with thiamine hydrochloride was followed by rapid recovery.

HIGGINS, Boston.

RECOGNITION OF ENCEPHALOCELES. L. W. VAN OUWERKERK, Nederl. tijdschr. v. geneesk. **90**:1147 (Sept. 14) 1946.

Only a few cases of encephalocele have been reported. The author describes the symptoms and diagnosis of encephalocele in 19 cases.

VAN CREVELD, Amsterdam, The Netherlands.

Diseases of the Ductless Glands; Endocrinology

FLUCTUATIONS IN WEIGHT, HEMATOCRIT AND PLASMA PROTEIN WITH THE MENSTRUAL CYCLE. D. N. DANFORTH, P. K. BOYER and SAMUEL GRAFF, Endocrinology **39**:188 (Sept.) 1946.

It is generally accepted that a significant increase in weight and, occasionally, manifest edema may occur in some women about the time of menstruation. These conditions have been attributed to a premenstrual retention of sodium, which is due to the action of the ovarian hormones. A tendency to an increase in blood sodium and chlorides during the midcycle has been reported, but there is no evidence of premenstrual elevation of these constituents in the circulating blood.

The present study was undertaken primarily to determine whether any gross fluctuations in blood electrolytes could be detected and correlated directly with alterations in weight.

It was found that the rise in the weight curve at about the time of menstruation is reflected by a simultaneous decline in the hematocrit reading. As one might expect, the protein curve is similar to the hematocrit curve. The latter curves might suggest a relative increase in blood volume at about the time of menstruation.

JACOBSEN, Buffalo.

IMMUNOLOGIC STUDIES IN INSULIN RESISTANCE: III. MEASUREMENT OF AN INSULIN ANTAGONIST IN THE SERUM OF AN INSULIN-RESISTANT PATIENT BY THE BLOOD SUGAR CURVE METHOD IN MICE. FRANCIS C. LOWELL, J. Clin. Investigation **26**:57 (Jan.) 1947.

Serum of an insulin-resistant patient with diabetes was studied for its insulin-interfering effect in mice.

This serum with the addition of 0.01 to 0.06 unit of insulin produced a rise in the average blood sugar of 8 mice thirty minutes after injection, with no significant fall in blood sugar after sixty minutes. When 0.005 to 0.01 unit of insulin was injected with normal serum, or with serum from an uncomplicated case of diabetes, a prompt fall occurred in the blood sugar at thirty minutes, which was sustained sixty minutes thereafter.

Titration of this neutralizing activity was attempted by mixing varying dilutions of the patient's serum with a constant dose of insulin. Mice given injections of serum in dilutions ranging from 1:3 to 1:24 with insulin showed no fall in blood sugar. When serum in the 1:48 dilution was injected, a pronounced drop in blood sugar occurred.

Quantitation of the degree of resistance to insulin was made as follows: Assuming that the insulin-neutralizing factor had a volume of distribution restricted to the circulating plasma, then the largest neutralizing dose per mouse (0.06 unit per 0.1 cc. of serum) times the volume of plasma (2,500 cc.) equaled the dose of insulin required to produce a fall in blood sugar.

This technic would appear to demonstrate the presence of an insulin-neutralizing antibody in the serum of this patient with insulin-resistant diabetes mellitus.

BRODSKY, Cincinnati.

HYPOGLYCEMIC SYNDROME IN AN INFANT WITH HYPERTROPHY OF THE THYMUS. A. CHIEFFI, Riv. di clin. pediat. **40**:401 (July) 1942.

The patient had had hypoglycemic crises from the age of 4 months; he died at the age of 18 months in hypoglycemic coma. Postmortem examination revealed pronounced hyperplasia of the thymus gland and hypoplasia of the adrenal medulla and the islands of Langerhans.

HIGGINS, Boston.

ANATOMICOPATHOLOGIC STUDY OF THYMOMAS. F. COLONNELLO, Riv. di clin. pediat. **40**:705 (Dec.) 1942.

A girl, 5½ years of age, had been ill for fifteen days with cough, dyspnea, orthopnea and fever; she died shortly after admission to the hospital. Autopsy revealed a tumor of the thymus weighing 550 Gm. The tumor resembled a lymphosarcoma. An extensive review of the literature on thymomas is given.

HIGGINS, Boston.

ACTION OF PANTOTHENIC ACID IN DIABETIC CHILDREN. L. NASSI, Riv. di clin. pediat. **41**:381 (July) 1943.

Studies on normal and diabetic children indicate that pantothenic acid increases and prolongs the hypoglycemic action of insulin.

HIGGINS, Boston.

THE THYMUS AND ITS INFLUENCE ON SUGAR METABOLISM. P. PROSPERI, Riv. di clin. pediat. **41**:497 (Oct.) 1943.

This paper gives a review of the literature on the thymus gland and contains an extensive bibliography.

HIGGINS, Boston.

Diseases of Muscles, Bones, Joints and Lymph Glands

SIMULTANEOUS OCCURRENCE OF SARCOIDOSIS (BOECK'S SARCOID) AND PRIMARY CHRONIC POLYARTHRITIS (BEGINNING SJÖGREN'S SYNDROME). E. ZWEIFEL, Helvet. pædiat. acta **1**:475 (Oct.) 1946.

A case of typical chronica rheumatica polyarthritis in a 10 year old girl is reported. The disease apparently began when she was 4 years of age and developed slowly. The first sign of sarcoidosis (Boeck's sarcoid) occurred at the age of 7 with inflammation of the eye, followed by hypopyon, keratitis and iritis, parotitis, Boeck's disease and lymphadenitis, hyperplasia of the spleen, sarcoid-like erythroderma and a diffuse (noncystic) epithelioid cell granulomatosis of the bone marrow.

As it is unlikely that a child as young as this patient would have two independent severe chronic diseases, the case reported, in view of all its symptoms, may perhaps be considered as *forme fruste* of Sjögren's syndrome, thus explaining the simultaneous existence of Boeck's disease, chronic polyarthritis, glossitis, a positive reaction to the Takata-Ara test and modifications in the albumin-globulin quotient.

The case is also worth recording because of the therapeutic success with blood transfusions.

FROM THE AUTHOR'S SUMMARY.

ESSENTIAL MUSCULAR HYPOTONIA IN DEGENERATE CHILDREN. HANS ZELLWEGER, Helvet. pædiat. acta **1**:495 (Oct.) 1946.

The author reports on several cases of hypotonia, observed especially in small children, which had shown little improvement at the time of his report. The condition in these cases was considered as a benign general weakness of the muscles of unknown origin or as an abortive form of amyotonia congenita (Oppenheim's disease), pseudohypertrophic muscular dystrophy (Erb's dystrophy) or hereditary familial spinal muscular atrophy (Hoffmann-Werdnig syndrome). It was observed that all the patients with hypotony showed one or several degenerative stigmas, especially signs of vegetative lability, diminished resistance to infections and abnormal psychic reactions. Their weights and heights varied from the average to a greater degree than those of nonhypotonic children. Such patients often came from families in which there were psychoses, psychopathy and increased mortality from tuberculosis. Much evidence is in favor of the theory that there is a constitutional deficiency in these degenerative hypotonic children.

FROM THE AUTHOR'S SUMMARY.

PROGRESSIVE OSSIFYING MYOSITIS: REPORT OF A CASE. IHSAN HILMI ALANTAR, Helvet. pædiat. acta **1**:505 (Oct.) 1946.

A case of progressive ossifying myositis in an 8 year old girl is reported. The disease began two years prior to the author's report in the cervical muscular apparatus and later extended to various muscles of the body, particularly those of the chest, upper arm and back. While the patient was under observation, new foci of the disease developed in the left pectoralis major muscle. Fever and pain accompanied these onsets; after subsidence of the fever there was ossification in the affected parts. Exploratory excisions from the various muscles affected showed degenerative hyperplasia and, in places, formation of bone in the intermuscular and intramuscular connective tissue. Nothing abnormal was observed in other organs, and there was no family history of similar cases. Doubtless the disease is due to a congenital embryonic disturbance. Although the onset of the disease is characterized by symptoms similar to those following inflammatory processes, it seems more correct to consider degenerative processes as the basis of the disease

FROM THE AUTHOR'S SUMMARY.

Book Reviews

Practical Physiological Chemistry. By Philip B. Hawk, Bernard L. Oser and William H. Summerson. Twelfth edition. Price, $10. Pp. over 1300. Philadelphia: The Blakiston Company, 1947.

A review of this book, a standard classroom text, might have been adequate under ordinary circumstances had it listed the merits and deficiencies of fact, style and format. However, this edition is marked by a rewriting of many chapters and by a change in authors. Comparison with previous editions reveals this one to be more comprehensive and more penetrating, in keeping with the rapid development in many fields of biochemistry. The general betterment is nearly matched by the introduction and able discussion of important technics; the sections on the Barcroft-Warburg apparatus, on photometry, and on antibiotics being especially noteworthy.

Certain factual details deserve emphasis. The book wisely refrains from an explanation of the mechanism of enzyme reactions, which at this time is largely a matter of speculation. The description of each photometric method is accompanied by the appropriate curve for absorption of radiant energy. Useful tables are plentiful, and include several new ones on hormones and enzyme classification and an appendix containing dietary allowances and composition of foods. Of particular interest to physicians will be the sound discussion of office hemoglobinometers.

The style of the book is uneven. Perhaps this defect is unavoidable in a book which has many contributors, some acknowledged and some, regrettably, not. The senior author refers all too frequently to his seniority, and is overly sentimental in the preface while ignoring completely the help of his erstwhile colleague, Professor Bergeim. Of lesser moment is the use of the confusing term "energy metabolism," as though energy were synthesized and disintegrated like proteins, fats and substances generally!

The print and paper are of good quality. The binding is poor, if the reviewer's copy is a representative sample.

The Biology of Stomach Kathepsin. By Dr. Med. S. Buchs. Price, 12 Swiss francs. Pp. 79, with 60 illustrations. Basel, Switzerland: S. Karger, 1947.

This monograph gives an excellent description of protein digestion in the stomach and does so in a manner which is instructive for the specialist in this field and yet understandable for the reader not specially trained. The first part of the book tries to prove the existence and to establish the identity of kathepsin as part of the enzyme system of the stomach. The discrepancy of the optimal acidity for pepsin action and the actual acidity of the chymus demand as explanation for the digestive process a second enzyme with the optimal activity more on the alkaline side. The author describes an accurate method of measuring the digestive process and then proceeds to analyze this "second ferment" as to its characteristics. He studies the enzyme action under different hydrogen ion concentrations and temperatures and under the influence of irradiation or activating or inhibiting sub-

stances. In the next chapter the action of kathepsin under varying conditions as to quantity, concentration, temperature and time of action is discussed and compared with the behavior of other known ferments. In order to establish fully the identity of kathepsin, its relationship to chymosin and its presence in animals were investigated. An analysis of reports of the literature shows that the presence of this enzyme has been overlooked by previous investigators and explains the reason for this. A chemical separation of the enzymes was never possible. A biologic separation of action was accomplished by inhibition of all but one ezyme action. The theory that the stomach protease is *one* enzyme with different actions under different chemical and physical conditions is considered favorably by the author. Katheptic and peptic action, as measured by biologic units, was found lowest in infants and highest in adults. Hydrochloric acid concentrations paralleled the enzyme concentrations in different persons under the same conditions, but not in the same person under different conditions (test meal). It was also felt that kathepsin continues its action in the duodenum, assisting the trypsin in much the same manner as it assists the pepsin in the stomach. The assumption of high alkalinity of duodenal chymus is as incorrect as the concept of high acidity of the stomach chymus. This rather gradual change of p_H of chymus makes it plausible that the opening of the pylorus is not a chemical reaction of the duodenum, but is regulated by the stomach.

In summarizing, it is stated that the protein digestion is least effective five to ten minutes after food intake, when the chymosin action starts. The next step is lipolysis, which in turn produces fatty acids. With increased acidity kathepsin reaches its maximum activity, and after part of the chymus has been expelled into the duodenum the pepsin action is highest. The booklet is plentifully supplied with technical descriptions of working methods, with illustrations and graphic charts and tables, as well as an extensive bibliography.

Medical Education and the Changing Order. Raymond B. Allen, M.D., Ph.D. Price, $1.50. Pp. 142. New York: Commonwealth Fund, 1946.

This little volume is one of a series of timely monographs sponsored by the Committee on "Medicine and the Changing Order" of the New York Academy of Medicine. Its author, until recently Dean of the University of Illinois Medical School (now President of the University of Washington), writes with a special degree of authority on the subjects discussed in his book because he received thorough training in both the clinical and the scientific aspects of medicine before embarking on his final career as a medical educator.

In the reviewer's opinion, this is the most significant single publication on the subject of medical education that has appeared during the last three decades. It could be read with profit by any physician or educator who is at all interested in medical progress. It deals succinctly with the developmental aspects of medical education, research and practice in the past and points out the new challenge facing the present day medical educator as a result of revolutionary social, economic and technologic changes.

The ever increasing demands on the time of the student and on the resources of medical schools and hospitals as a result of rapid advances in our scientific knowledge and technical processes require constant readjustment and reorganization

of the curriculum if medical education is to meet the challenge and live up to its responsibilities and opportunities. It is pointed out that the physician of the future cannot be a mere technologist or tradesman, if he is to make the most of his career, but must recognize the fact that the health of his patients and of the community as a whole has numerous social implications. As a highly respected and privileged member of society, the physician must assume a share of the leadership of his community in all civic matters which have to do with the prevention of disease or disability of any kind. Medical education, according to the author's thesis, should assume responsibility for giving the medical student this social orientation in addition to providing him with the best opportunity possible to acquire the essential knowledge and technical skills required for successful practice of preventive and curative medicine.

The importance of graduate training and of postgraduate courses for physicians is likewise stressed. As regards the more specific methodology of medical education, Dr. Allen emphasizes the need for better recognition of the good teacher by medical schools. He decries the tendency for overemphasis on education at the departmental as opposed to the total school or faculty level.

His references to the physician's relationships to society and his responsibilities as regards medical care for all of our people are well summarized in the following paragraph:

"Physicians of the future must be capable of taking their places as responsible leaders in the community and of viewing the problems of medical service dispassionately. Unless they recognize the right of every person to adequate medical service the medical profession will degenerate to the level of a trade in which, as tradesmen, physicians will be concerned merely with the technique of their trade. The medical profession cannot assume full responsibility for supplying complete medical service everywhere; it is no more responsible for the inadequacy of medical service in certain economically depressed regions of the country than teachers are responsible for the high illiteracy rates which are often found in the same places. It is under obligation, however, to cooperate fully with voluntary and public agencies so that together they may create the economic and social conditions which make possible an adequate medical service for all."

Vocational and Professional Monographs—Physiotherapy. Thomas Francis Hennessey, M.D. Price, $0.75. Pp. 20. Boston: Bellman Publishing Company, Inc., 1946.

Recognition of the increasing value of physical procedures has today reached the stage where virtually every specialty makes use of its therapeutic properties. Under the circumstance the great demand is for expositions that offer clear and detailed information that will not only bridge the gap between pharmacologic and physical agents but will provide a logical synthesis for its intelligent use in medical practice. Accordingly, the current need is for texts and monographs of more detailed substance than is usually provided by such abbreviated efforts associated with publications of paper-covered brochures. To be sure, such contributions have their place in scientific literature, especially when the contents of information outweigh the heft of dull tomes. And while one will readily acknowledge that literary

nuggets may be often found in both types of treatises, it is clearly illogical to expect to find the essential meat and substance of either theory or practice on physical medicine in a 20 page booklet which offers but the barest skeletonized exposition on this discipline. The discourse is as limited in information as the outline of some table of contents found in some of the more ambitious texts on the subject, or as sterile as an index separated from its context.

Skin Diseases, Nutrition and Metabolism. Erich Urbach, M.D. Price, $10. Pp. 640, with 266 illustrations and 112 tables. New York: Grune & Stratton, 1946.

This book fills a much neglected void in discussing the nutritional and metabolic aspects of cutaneous disease. Much has been written of the relationship between dermatology and general medicine, and in this volume a definite contribution to this field has been made by this exposition of the basic metabolic and nutritional factors of the skin and its diseases. The book has been divided into five parts.

Part I deals with the influence of the basic principles of nutrition on the function of the skin. The fundamentals of water, mineral, carbohydrate, lipid and protein metabolism are reviewed in the first section of this part. In the second section the influence of various diets on the metabolism of the skin is discussed. Consideration is given not only to low and high carbohydrate, fat and protein diets but to acidifying, dehydration, low sodium chloride and low potassium diets and other possible variations.

Part II considers the nutritional causes of dermatoses, both the quantitative causes, or overnourishment and undernourishment, and the qualitative causes. The latter group, the specific causes, deals in considerable detail with the various deficiencies due to lack of carbohydrate, proteins, fats and the various vitamins. Among these nutritional causes of cutaneous disease, allergy due to foods is given much space. The various food allergens are given consideration, as well as diagnosis and treatment, including desensitization. While the author approves in general the use of the scratch test and the passive transfer method of testing, he registers his disapproval of the intracutaneous tests in these cases. This view is shared by many other authorities. The author fails to outline his criteria and technic of cutaneous tests, although he details the technic of the passive transfer method. It is emphasized that skin tests, trial diets, elimination diets and "propetan" diets are useful diagnostic methods along with a careful detailed history. The latter is still an important factor. "Propetans" are food digests derived from individual foods through prolonged digestion with hydrochloric acid and pepsin, followed by some additional digestion with trypsin. It is the author's claim that the specific food digest taken forty-five minutes previous to ingestion of the particular allergen food is valuable in both diagnosis and therapy.

In Part III is discussed the influence of diseases of the gastrointestinal tract, liver and pancreas on the skin. There is also a discussion of the disturbances of these organs due to cutaneous disease.

In Part IV the nutritional therapy of cutaneous diseases is elaborated in considerable detail. Each of many skin diseases is discussed from the standpoint of diet and of vitamin therapy.

Part V has numerous nutritional tables. There are age and weight tables, quick reference conversion tables (pounds to kilograms, inches to centimeters, etc.), tables of composition of foods, types of food, dietary sources of mineral constituents of foods, elimination diets, etc.

The book is well documented with over 1,300 references. The opinions of both sides of numerous controversial questions are often quoted, with the author often expressing his opinion from his own personal experience. The printing is excellent, and there are numerous excellent clinical photographs. In many instances there are before and after photographs showing the effect of a particular diet or vitamin therapy Throughout the volume are numerous tables indicating sample diets for a particular disease, as well as tables of food of a particular composition, low fat, high protein, wheat free, etc.

For the pediatrician there is considerable of interest. There is a fair-sized section on infantile eczema and seborrheic eczema, with good illustrations. Acne, psoriasis and the vitamin deficiencies are also well discussed from the nutritional angle, and there are numerous references to the dietary and vitamin therapy oi infants and young adults in the various parts of the book.

Directory of Pediatric Societies *

INTERNATIONAL

International Association of Preventive Pediatrics

President: Prof. S. Monrad, Dronning Louises Børnehospital, Copenhagen, Denmark.
Secretary: Dr. Daniel Oltramare, 15 Rue Lévrier, Geneva, Switzerland.

International Congress of Pediatrics

President: Dr. Henry F. Helmholz, Mayo Clinic, Rochester, Minn.
Secretary-General: Dr. L. Emmett Holt Jr., 477 First Ave., New York 16.
Canadian Committee:
Chairman: Dr. Alan Brown, Hospital for Sick Children, 67 College St., Toronto 2.
Secretary: Dr. S. G. Ross, 1390 Sherbrooke St. W., Montreal.

International Congress for the Protection of Infancy

Secretary: Prof. G. B. Allaria, Corso Bramante 29, Torino 120, Italy.

Pan American Congress of Pediatrics

President: Dr. Felix Hurtado, Habana, Cuba.

Save the Children International Union

President: Mrs. Gordon Morier.
Secretary: Dr. Georges Thélin, 43 Quai Wilson, Geneva, Switzerland.

FOREIGN

Argentine Pediatric Society of Buenos Aires

President: Dr. Martin Ramón Arana, 1809 Rodriguez Peña, Buenos Aires.
General Secretary: Dr. Alfredo Larguia, Cerrito 1179, Buenos Aires.

Associação Paulista de Medicina, Secçaõ de Pediatrias

President: Dr. Vicente Lara.
First Secretary: Dr. Armando de Arruda Sampaio.
Second Secretary: Dr. Luiz Augusto Monteiro Toledo, Av. Brigadeiro Luiz Antonio 393, 1° Andar, São Paulo, Brazil.
Time: Twelfth of every month, 8:30 p. m.

British Paediatric Association

President: Prof. G. B. Fleming, 13 Lynedoch Crescent, Glasgow.
Joint Secretary: Prof. Alan Moncrieff, Hospital for Sick Children, Great Ormond St., London, W. 1.

Danish Pediatric Society

President: Prof. E. Lenstrup, Copenhagen.
Secretary: Dr. Gjørup, Dronning Louises Børnehospital, Copenhagen.

Nederlandische Vereeniging voor Kindergeneeskunde

President: Dr. J. L. Keyzer, 114 St. Josephstr., Tilburg.
Secretary: Dr. H. Reerink, 2B Paul Krugerstr., Arnheim.
Place: Children's Hospital or Pediatric Clinic. Time: Three times a year.

* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

PALESTINE JEWISH MEDICAL ASSOCIATION, SECTION OF PHYSICIANS OF CHILDREN'S DISEASES

President: Prof. L. F. Meyer, 29 Toelsohn St., Tel Aviv.
Secretary: Dr. A. Brünn, 9 Maazestre, Tel Aviv.

ROYAL SOCIETY OF MEDICINE, SECTION FOR THE STUDY OF DISEASES IN CHILDREN

President: Dr. W. G. Wyllie, 33 Wimpole St., London W. 1, England.
Secretary: Dr. Philip Rainsford Evans, Keat's House, Guy's Hospital, London S. E. 1, England.
Place: 1 Wimpole St., London W. 1. Time: Fourth Friday of each month, 4:15 p. m.

SOCIEDAD BOLIVIANA DE PEDIATRIA

President: Dr. Ernesto Trigo Pizarro.
Secretary: Dr. Carlos Ferrufino, Casilla 272, La Paz, Bolivia.
Place: La Paz, Bolivia.

SOCIEDAD CHILENA DE PEDIATRIA

President: Mr. Cesar Izzo Parodi, Merced 565, Santiago, Chile.
General Secretary: Dr. Jorge Peña Cereceda, Santiago, Chile.

SOCIEDAD CUBANA DE PEDIATRIA

President: Dr. Teodosio Valledor, Habana.
Secretary: Dr. Carlos Hernandez Miyares, Hospital Nuestra Señora de las Mercedes L y 21, Apartado 2430, Habana.
Place: Cátedra de Clinica Infantil, Hospital Nuestra Señora de las Mercedes y Hospital Municipal de Infancia, Habana. Time: Last Wednesday of every month.

SOCIEDAD DOMINICANA DE PEDIATRIA

President: Dr. Alberto Peguero, Ciudad Trujillo, R.D.
Secretary-Treasurer: Dr. Jaime Jorge, Ciudad Trujillo, R.D.
Place: Children's Ramfis Hospital. Time: 8 p. m., last Thursday of every month.

SOCIEDAD ECUADORIANA DE PEDIATRIA

President: Dr. Francisco de Icaza Bustamente.
Secretary: Dr. M. I. Gómez Lince, P. O. Box 693, Guayaquil.

SOCIEDAD MEXICANA DE PEDIATRIA

President: Dr. Antonio Prado Vértiz, Edison 101, Mexico City, Mexico.
Secretary: Dr. Manuel Mendez, Hospital del Niño Mexico City, Mexico.

SOCIEDAD DE PEDIATRÍA DE CÓRDOBA

President: Dr. Juan Francisco Herrera, Córdoba, Argentina.
Secretary: Dr. Bernardo Serebrinsky, Dean Funes 2000, Esq. Ocaña (N.), Córdoba, Argentina.
Place: Comite pro Defenso del Niño, Dean Funes 2000, Córdoba, Argentina. Time: Once a month.

SOCIEDAD DE PEDIATRIA DEL LITORAL

President: Dr. Jose E. Celoria, Hospital Centenario, Rosario, Argentina.
Secretary: Dr. Gloria Lovell, Hospital Centenario, Rosario, Argentina.

SOCIEDAD DE PEDIATRÍA DE SANTIAGO DE CUBA

President: Dr. Antonio Béguez César, Sagarra 107, Santiago de Cuba.
Secretary: Dra. Susana Texdó Vaillant, Padre Pico 57, Santiago de Cuba.
Place: Colegio Médico. Time: Last Tuesday of every month.

SOCIEDAD VENEZOLANA DE PUERICULTURA Y PEDIATRIA

President: Dr. Pastor Oropeza, Caracas.
Secretary: Dr. Carlos E. Castillo, Hospital Municipal de Niños, Caracas.
Place: Hospital Municipal de Niños Jose Manuel de los Rios, Caracas.

SOCIÉTÉ DE PÉDIATRIE DE PARIS

President: Dr. G. Heuyer, 1 Ave. Emile Deschanel, Paris 7e, France.
Secretary: Dr. Maurice Lamy, 94 rue de Varenne, Paris 7e, France.
Place: Hôpital des Enfants Maladies, 149 Rue de Sèvres. Time: 4:30 p. m., third Thursday of every month.

SWEDISH MEDICAL SOCIETY, SECTION FOR PEDIATRICS AND SCHOOL HYGIENE

President: Prof. Arvid Wallgren, 53 Strandvägen, Stockholm.
Secretary: Dr. Henning Magnusson, 58 Odengatan, Stockholm.
Place: Various clinics and hospitals in Stockholm and Uppsala. Time: Second Friday of each month (except summer).

URUGUAYAN SOCIETY OF PEDIATRICS

President: Dr. Jose Bonaba, Montevideo.
Secretary: Dr. Héctor Fossatti, Durazno 1882, Montevideo.
Place: Club Medico del Uruguay, Avenda Agraciado 1464 (Piso 13), Montevideo.

NATIONAL

AMERICAN MEDICAL ASSOCIATION, SCIENTIFIC ASSEMBLY, SECTION ON PEDIATRICS

Chairman: Dr. Oscar Reiss, 2200 W. 3d St., Los Angeles.
Secretary: Dr. Margaret Mary Nicholson, 1801 Eye St. N. W., Washington, D. C.
Place: Chicago. Time: June 21-25, 1948.

AMERICAN ACADEMY OF PEDIATRICS

President: Dr. Jay I. Durand, 515 Cobb Bldg., Seattle, Wash.
Secretary: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.
Place: Atlantic City, N. J. Time: Nov. 20-23, 1948.
Regional Meetings:
Place: Milwaukee, Wis. Time: June 28-30, 1948.
Place: Seattle, Wash. Time: Sept. 13-15, 1948.

AMERICAN HOSPITAL ASSOCIATION, MASSACHUSETTS HOSPITAL ASSOCIATION

Chairman: Dr. Frank Wing, Boston.
Secretary: Dr. W. Franklin Wood, McLean Hospital, Waverly 79, Mass.

AMERICAN PEDIATRIC SOCIETY

President: Dr. Harold K. Faber, 2361 Clay St., San Francisco.
Secretary-Treasurer: Dr. Henry G. Poncher, 1819 W. Polk St., Chicago 12.

CANADIAN SOCIETY FOR THE STUDY OF DISEASES OF CHILDREN

President:: Dr. Alan Ross, 1414 Drummond St., Montreal.
Secretary-Treasurer: Dr. R. L. Denton, 3534 Ontario Ave., Montreal.

SOCIETY FOR PEDIATRIC RESEARCH

President: Dr. Donovan J. McCune, 3975 Broadway, New York.
Secretary: Dr. Robert Ward, Bellevue Hospital, New York 16.

SECTIONAL

INTERMOUNTAIN PEDIATRIC SOCIETY

President: Dr. Wesley H. Anderson, 2404 Washington Blvd., Ogden, Utah.
Secretary-Treasurer: Dr. F. M. Kriete, State Capitol, Salt Lake City.
Place: Salt Lake City General Hospital. Time: First Thursday of each month, 8 p. m.

New England Pediatric Society

President: Dr. James Marvin Baty, 1101 Beacon St., Brookline, Mass.
Secretary-Treasurer: Dr. Charles D. May, 300 Longwood Ave., Boston
Place: Boston Medical Library. Time: Three meetings a year, occurring from September to May.

North Pacific Pediatric Society

President: Dr. Percy Guy, 502–2d Ave., Seattle, Wash.
Secretary: Dr. Aldis B. Johnson, 515 Cobb Bldg., Seattle, Wash.

Northwestern Pediatric Society

President: Dr. George Kimmel, Redwing, Minn.
Secretary-Treasurer: Dr. Northrop Beach, 1009 Nicollet Ave., Minneapolis.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

Rocky Mountain Pediatric Society

President: Dr. Jackson L. Sadler, 109 W. Olive St., Ft. Collins, Colo.
Secretary: Dr. Edwin T. Williams, 1850 Gilpin St., Denver 6.

Southern Medical Association, Section of Pediatrics

Chairman: Dr. Stewart H. Welch, 117 S. 20th St., Birmingham 5, Ala.
Secretary: Dr. W. Ambrose McGee, 1601 Monument Ave., Richmond 20, Va.

STATE

Alabama Pediatric Society

President: Dr. Ruth Berrey, 2211 Highland Ave., Birmingham 5, Ala.
Secretary-Treasurer: Dr. W. A. Daniel Jr., 115 S. Union St., Montgomery 5, Ala.
Place: Birmingham. Time: September 1948.

Arizona Pediatric Society

President: Dr. W. P. Sherrill, 342 W. McDowell Rd., Phoenix.
Secretary: Dr. W. F. Schoffman, 926 E. McDowell Rd., Phoenix.
Place: Phoenix or Tucson. Time: At time of state meeting.

Arkansas State Pediatric Association

Chairman: Dr. C. B. Billingsley, 1425 N. 11th St., Fort Smith.
Secretary: Dr. R. E. Weddington, 1425 N. 11th St., Fort Smith.

California State Medical Society, Section on Pediatrics

Chairman: Dr. Charles W. Leach, 2000 Van Ness Ave., San Francisco 9.
Secretary: Dr. Chester I. Mead, 1930 Truston Ave., Bakersfield.

Florida State Pediatric Society

President: Dr. James R. Boulware, Lakeland.
Secretary: Dr. Hugh A. Carithers, 2000 Park St., Jacksonville 4.
Place: Concurrent with state association convention and fall meeting.

Georgia Pediatric Society

President: Dr. Alton Johnson, 102 E. Central Ave., Valdosta.
Secretary-Treasurer Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.
Place: Atlanta. Time: At time of annual state meeting.

Hezekiah Beardsley Pediatric Club of Connecticut

President: Dr. F. M. Meyer, 144 Golden Hill St., Bridgeport, Conn.
Secretary: Dr. Herman Yannet, Southbury Training School, Southbury.

Illinois State Medical Society, Section on Pediatrics

Chairman: Dr. Frederick H. Maurer, 331 Fulton St., Peoria 2.
Secretary: Dr. Eugene T. McEnery, 4458 W. Madison St., Chicago.

Indiana State Pediatric Society

President: Dr. K. T. Knode, 1105 E. Jefferson Bldg., South Bend.
Secretary-Treasurer: Dr. Matthew Winters, 621 Hume Mansur Bldg., Indianapolic.
Time: Two meetings a year.

Iowa Pediatric Society

President: Dr. Arnold M. Smythe, 406–6th Ave., Des Moines.
Secretary-Treasurer: Dr. James Dunn, 414 Blackhawk Hotel, Davenport.

Louisiana State Pediatric Society

President: Dr. R. V. Platou, 1430 Tulane Ave., New Orleans 13.
Secretary-Treasurer: Dr. Bertha Wexler, 3439 Prytania St., New Orleans 15.

Medical Society of the State of Pennsylvania, Pediatric Section

Chairman: Dr. Carl H. Laws, 12 Pierrepont St., Brooklyn, N. Y.
Secretary: Dr. George R. Murphy, 292 Madison Ave., New York.

Medical Society of the State of Pennsylvania, Pediatric Section

Chairman: Dr. Joseph A. Gilmartin, 3700–5th Ave., Pittsburgh 13.
Secretary: Dr. Carl C. Fischer, 100 W. Coulter St., Philadelphia 44.

Michigan State Medical Society, Pediatric Section

Chairman: Dr. J. H. Lewis, 2956 Biddle Ave., Wyandotte.
Secretary: Dr. Robert H. Trimby, 122 W. Hillsdale, Lansing.

Mississippi State Pediatric Society

President: Dr. Harvey F. Garrison Jr., 315 E. Capitol Pl., Jackson.
Secretary: Dr. Guy Verner, 126 N. Congress St., Jackson.

Nebraska Pediatric Society

President: Dr. Paul N. Marrow, 1614 Medical Arts Bldg., Omaha 2.
Secretary-Treasurer: Dr. Michael Crofoot, 1407 Medical Arts Bldg., Omaha 2.
Place: As announced by committee. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

New Mexico State Pediatric Society

President: Dr. M. K. Wylder, 221 W. Central Ave., Albuquerque.
Secretary-Treasurer: Dr. Ly Werner, 221 W. Central Ave., Albuquerque.

North Carolina Pediatric Society

President: Dr. Charles R. Bugg, Professional Bldg., Raleigh.
Secretary: Dr. Charles F. Williams, 817 Hillsboro St., Raleigh.

Northern California Pediatric Society

President: Dr. Edith M. Meyers, 431–30th St., Oakland.
Secretary: Dr. A. L. Gleason, 411–29th St., Oakland 9.
Place: San Francisco. Time: Second Thursday of February, April, September and November.

Oklahoma State Pediatric Society

President: Dr. J. B. Snow, 625 N. W. 10th St., Oklahoma City.
Secretary: Dr. Bertha Levy, 1200 N. Walker St., Oklahoma City.
Place: With Oklahoma State Medical Association. Time: Annual Meeting.

South Carolina Pediatric Society

President: Dr. George D. Johnson, Spartanburg.
Secretary-Treasurer: Dr. B. O. Ravenel, Roper Hospital, Charleston.

Tennessee Pediatric Society

President: Dr. Harold J. Starr, 803 Medical Arts Bldg., Chattanooga 3.
Secretary-Treasurer: Dr. W. O. Vaughan, 2105 Hayes St., Nashville 5.
Time: Second Monday in April.

Texas Pediatrc Society

President: Dr. Charles B. Alexander, 1716 Nix Professional Bldg., San Antonio 5.
Secretary-Treasurer: Dr. John E. Ashby, 3610 Fairmount Ave., Dallas 4.

Virginia Pediatric Society

President: Dr. Thomas Gibson, 114 W. Boscawen St., Winchester.
Secretary: Dr. E. Berkeley Neal, 303 Washington Ave. S. W., Roanoke.

West Virginia State Medical Society, Section on Pediatrics

President: Dr. Jack Basman, 1021 Quarrier St., Charleston.
Secretary: Dr. Harry E. Baldock, Medical Arts Bldg., Charleston.

Wisconsin State Medical Society, Section on Pediatrics

Chairman: Dr. M. G. Peterman, 411 E. Mason St., Milwaukee 2.
Secretary: Dr. L. M. Simonson, 1001 N. 8th St., Sheboygan.

LOCAL

Academy of Medicine of Cleveland, Pediatric Section

Chairman: Dr. J. I. Hartman, 10515 Carnegie Ave., Cleveland.
Secretary: Dr. Alexander N. Freed, 2012 W. 25th St., Cleveland.
Place: Cleveland Medical Library Bldg. **Time:** 8:15 p. m., October, December, February and April.

Academy of Medicine, Toronto, Section of Pediatrics

President: Dr. J. H. Ebbs, 13 Queen's Park, Toronto, Canada.
Secretary: Dr. J. F. McCreary, 170 St. George St., Toronto, Canada.
Place: Academy of Medicine. **Time:** 8:30 p. m., third Thursday of each month.

Baltimore City Medical Society, Pediatric Section

Chairman: Dr. Charles O'Donovan Jr., 5 E. Read St., Baltimore.
Secretary: Dr. T. Campbell Goodwin, 16 E. Biddle St., Baltimore.

Bronx Pediatric Society

President: Dr. Harry S. Pizer, 1726 Davidson Ave., New York.
Secretary: Dr. Nathan M. Greenstein, 1488 Metropolitan Ave., New York.
Place: Morrisania City Hospital. **Time:** 8:30 p. m., second Wednesday of each month, except June, July, August and September.

Brooklyn Academy of Pediatrics

President: Dr. George E. Brockway Jr., 176 Fenimore St., Brooklyn.
Secretary: Dr. Bernard Benjamin, 845 Park Pl., Brooklyn 16.
Place: Granada Hotel. **Time:** 8:45 p. m., fourth Wednesday of February, March, April, October and November.

Buffalo Pediatric Society

President: Dr. Douglas P. Arnold, 159 Bidwell Parkway, Buffalo, N. Y.
Secretary: Dr. Richard A. Downey, 786 Forest Ave., Buffalo 9, N. Y.
Place: Children's Hospital, 219 Bryant St. **Time:** 8:30 p. m., first Monday of each month from September to June.

Central New York Pediatric Club

President: Dr. Arthur W. Benson, 2 St. Paul St., Troy.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Places: Various cities in New York. Time: Third Tuesday of April and October.

Chicago Pediatric Society

President: Dr. H. William Elghammer, 2371 E. 71st St., Chicago.
Secretary: Dr. Alvah L. Newcomb, 723 Elm St., Winnetka, Ill.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May inclusive.

Cincinnati Pediatric Society

President: Dr. Leo S. Friedman, 666 Rockdale Ave., Cincinnati 29.
Secretary: Dr. George Renner, 3144 Jefferson Ave., Cincinnati.
Place: Children's Hospital, Elland Ave., Cincinnati. Time: On call.

Dallas Pediatric Society

President: Dr. Shirley Hodges, 2703 Oak Lawn Ave., Dallas, Texas.
Secretary-Treasurer: Frances M. Love, 4585 Belfort, Dallas 4.
Place: Children's Medical Center. Time: 1 p. m., third Saturday and 8:30 p. m., the first Thursday of each month.

Detroit Pediatric Society

President: Dr. Otto Grob, 651 Fisher Bldg., Detroit 2, Mich.
Secretary: Dr. Harold B. Rothbart, 773 Fisher Bldg., Detroit 2, Mich.
Place: Variable. Time: Third Wednesday of each month.

Houston Pediatric Society

President: Dr. George Salmon, 1220 Bartlett St., Houston, Texas.
Secretary: Dr. Betty Moody, 526 Richmond Rd., Houston, Texas.
Place: River Oaks Country Club. Time: 7:30 p. m., last Tuesday of each month.

Kansas City (Missouri) Pediatric Society

President: Dr. Harry M. Gilkey, 1624 Professional Bldg., Kansas City.
Secretary: Dr. Leland Speer, 1022 Parkway, Kansas City.
Place: Kansas City General Hospital. Time: On call.

Knoxville–Oak Ridge Pediatric Society

President: Dr. Henry S. Christian, 205 Medical Arts Bldg., Knoxville, Tenn.
Secretary: Dr. John Eggleston, Oak Ridge Hospital, Oak Ridge, Tenn.

Los Angeles County Medical Association, Pediatric Section

President: Dr. Elena Boder, 1830½ Lucille Ave., Los Angeles 26.
Secretary-Treasurer: Dr. Robert Simonds, 267 S. Beverly Dr., Beverly Hills, Calif.
Place: Los Angeles County Medical Association Bldg., 1925 Wilshire Blvd. Time: Second Monday of February, April, June, October and December.

Medical Society of the County of Kings and the Academy of Medicine of Brooklyn, Pediatric Section

President: Dr. Samuel K. Levy, 1694 Nostrand Ave., Brooklyn 26.
Secretary: Dr. Samuel Silber, 865 Park Pl., Brooklyn 16.
Place: 1313 Bedford Ave., Brooklyn. Time: 9:00 p. m., fourth Monday of each month.

Medical Society of the County of Queens, Inc., Section on Pediatrics

Chairman: Dr. Meyeron Coe, 217-02–91st Ave., Queens Village, N. Y.
Secretary-Treasurer: Dr. Louis Appel, 143-42 Cherry Ave., Flushing, N. Y.
Place: Queens County Medical Bldg., Forest Hills, N. Y. Time: Third Monday of October, January, March and May.

MEDICAL SOCIETY OF THE DISTRICT OF COLUMBIA, SECTION ON PEDIATRICS

President: Dr. John Washington, 2203 Wyoming Ave., Washington, D. C.
Secretary-Treasurer: Dr. George Maksim, 1418 Good Hope Rd. S.E., Washington, D. C.
Place: Medical Society Bldg., 1718 M St. N. W. Time: 8 p. m., third Thursday of October, January, March and May.

MEMPHIS PEDIATRIC SOCIETY

President: Dr. Kinsey M. Buck, 1193 Madison Ave., Memphis, Tenn.
Secretary-Treasurer: Dr. Barton Etter, 1024 Madison Ave., Memphis, Tenn.

MILWAUKEE PEDIATRIC SOCIETY

President: Dr. M. G. Peterman, 411 E. Mason St., Milwaukee 2, Wis.
Secretary-Treasurer: Dr. Katharine Baird, 1411 Wauwatosa Ave., Wauwatosa 13, Wis.
Place: Milwaukee Children's Hospital. Time: Second Wednesday in February, April, June, October and December.

NEW YORK ACADEMY OF MEDICINE, SECTION OF PEDIATRICS

Chairman: Dr. Harold W. Dargeon, 1095 Park Ave., New York.
Secretary: Dr. John Dorsey Craig, 120 E. 75th St., New York 21.
Place: New York Academy of Medicine, 2 E. 103d St. Time: Second Thursday of each month from November to May, inclusive, 8:30 p. m.

OKLAHOMA CITY PEDIATRIC SOCIETY

President: Dr. J. B. Snow, 625½ N. W. 10th St., Oklahoma City.
Secretary: Dr. Bertha Levy, 1200 N. Walker St., Oklahoma City.
Place: Oklahoma Club. Time: Third Thursday of each month.

PHILADELPHIA PEDIATRIC SOCIETY

President: Dr. Arthur M. Dannenburg, 235 S. 15th St., Philadelphia 2.
Secretary: Dr. D. Stewart Polk, Rosemont, Pa.
Place: College of Physicians, 19 S. 22d St. Time: 8:30 p. m., second Tuesday from October to May, inclusive.

PITTSBURGH PEDIATRIC SOCIETY

President: Dr. Elwood Stitzel, 403 Central Trust Bldg., Altoona, Pa.
Secretary-Treasurer: Dr. C. J. Stoecklein, Medical Arts Bldg., Pittsburgh 13.
Place: Pittsburgh Academy of Medicine. Time: Second Friday in October, December, February and April.

RICHMOND PEDIATRIC SOCIETY

President: Dr. Edwin L. Kendig Jr., 828 W. Franklin St., Richmond 20, Va.
Secretary-Treasurer: Dr. Thomas S. Chalkley, 1200 E. Broad St., Richmond, Va.
Place: Medical College Hospital. Time: 8 p. m., third Thursday of each month, except June, July and August.

ROCHESTER PEDIATRIC SOCIETY

President: Dr. Jerome Glaser, 300 S. Goodman St., Rochester 7, N. Y.
Secretary-Treasurer: Dr. Daniel B. Peeler, 1162 Lake Ave., Rochester 13, N. Y.
Place: Rochester Academy of Medicine or arrangement by program committee.
Time: Third Friday of each month from October to May.

ST. LOUIS PEDIATRIC SOCIETY

President: Dr. Joseph C. Jaudon, 337 N. Euclid Ave., St. Louis.
Secretary-Treasurer: Dr. Gilbert B. Forbes, 500 S. Kingshighway, St. Louis 10.
Time: Second Thursday of each month from October to May, inclusive.

San Antonio Pediatric Society

President: Dr. Sidney R. Kaliski, 518 Moore Bldg., San Antonio 5.
Secretary-Treasurer: Dr. Edith M. Bonnet, 228 Medical Arts Bldg., San Antonio 5.
Place: Variable. Time: 7:30 p. m., first Tuesday of every month.

Seattle Pediatric Society

President: Dr. Sherod M. Billington, Medical Dental Bldg., Seattle 1.
Secretary: Dr. Jack M. Doctor, 738 Broadway, Seattle 22.
Place: College Club. Time: Fourth Friday of each month from September to June at 6:30 p. m.

Southwestern Pediatric Society

President: Dr. Donald C. Shelby, 416 N. Bedford Dr., Beverly Hills, Calif.
Secretary: Dr. Harry F. Dietrich, 416 N. Bedford Dr., Beverly Hills, Calif.
Place: University Club of Los Angeles. Time: 6:30 p. m., first Wednesday in January, March, May, September and November.

University of Michigan Pediatric and Infectious Disease Society

President: Dr. Park Bradshaw, Muskegon, Mich.
Secretary: Dr. Harry A. Towsley, 1313 E. Ann St., Ann Arbor, Mich.

Westchester County Medical Society, Pediatrics Section (New York)

President: Dr. John B. Ahouse, 27 Ludlow St., Yonkers, N. Y.
Secretary-Treasurer: Dr. Elvira Ostlund, 64 Highland Rd., Rye, N. Y.
Place: Hospitals of Westchester County. Time: Third Thursday in November, January, March and May.

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